NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

## Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

## Appraisal Committee Meeting – 10 July 2025

**First committee meeting:**

The following documents are made available to the committee attendees:

The **final scope** and **final stakeholder list** are available on the NICE website.

**Pre-technical engagement documents**

1. **Company submission summary** from Italfarmaco
2. **Company summary of information for patients (SIP)** from Italfarmaco
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Action Duchenne
   b. Duchenne UK (joint submission with Muscular Dystrophy UK)
   c. Muscular Dystrophy UK (joint submission with Duchenne UK)
   d. Association of British Neurologists
   e. British Paediatric Neurology Association
   f. British Society of Physical and Rehabilitation Medicine
   g. John Walton Muscular Dystrophy Research Centre
5. **External Assessment Report** prepared by Bristol Technology Assessment Group
6. **External Assessment Report – factual accuracy check**

**Post-technical engagement documents**

7. **Technical engagement response from company**
8. **Technical engagement responses and statements from experts:**
   a. Dr Anne-Marie Childs – clinical expert, nominated by Italfarmaco, Action Duchenne, Duchenne UK and Muscular Dystrophy UK
   b. Professor Tracey Willis – clinical expert, nominated by Italfarmaco and Muscular Dystrophy UK

c. Emma Hallam – patient expert, nominated by Duchenne UK and Muscular Dystrophy UK
d. Jack Johnson – patient expert, nominated by Muscular Dystrophy UK

**9. Technical engagement responses from stakeholders:**

a. Action Duchenne (joint response with Duchenne UK and Muscular Dystrophy UK)
b. Duchenne UK (joint response with Action Duchenne and Muscular Dystrophy UK)
c. Muscular Dystrophy UK (joint response with Action Duchenne and Duchenne UK)
d. Association of British Neurologists
e. John Walton Muscular Dystrophy Research Centre

**10. External Assessment Report critique of company response to technical engagement** prepared by Bristol Technology Assessment Group

a. EAG critique
b. EAG addendum post-technical engagement
c. Factual accuracy check of EAG critique

**Appraisal Committee Meeting presentation slides** – to follow

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Single technology appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over ID6323

# Document B

# Company evidence submission

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# Abbreviations

| | |
|---|---|
| 4SC | 4-stair climb |
| 6MWD | 6-minute walking distance |
| 6MWT | 6-minute walking test |
| 10MWT | 10-metre walking test |
| ADL | Activities of daily living |
| AE | Adverse event |
| AFT | Acceleration factor |
| ANCOVA | Analysis of covariance |
| bid | Twice daily |
| BMI | Body mass index |
| BNF | British National Formulary |
| BOI | Burden of illness |
| BSA | Body surface area |
| CAPE | Children's Assessment of Participation and Enjoyment |
| CEM | Cost-effectiveness model |
| CEAC | Cost-effectiveness acceptability curve |
| CHMP | Committee on Medicinal Products for Human Use |
| CI | Confidence interval |
| CINRG | Cooperative International Neuromuscular Research Group |
| CPRD | Clinical Practice Research Datalink |
| CRF | Case report form |
| CS | Corticosteroids |
| CSR | Clinical study report |
| DAPC | Dystrophin-associated protein complex |
| DCO | Data cut off |
| DMD | Duchenne muscular dystrophy |
| DMDSAT | Duchenne muscular dystrophy Functional Ability Self-Assessment Tool |
| DNHS | Duchenne Natural History Study |
| DoF | Data on file |
| DSU | Decision Support Unit |
| EAG | External Assessment Group |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECM | Established clinical management |
| EK | Egen Klassifikation |
| EMA | European Medicines Agency |
| EQ-5D-5L | European Quality of Life 5 dimensions 5 level version |
| ESS | Effective sample size |
| FEV1 | Forced expiratory volume in 1 second |
| FVC | Forced vital capacity |
| FVC<1L | Forced vital capacity <1 litre |
| GCS | Glucocorticosteroids |
| GI | Gastrointestinal |
| GLS | Generalised least squares |
| HAT | Histone acetyltransferases |
| HDAC | Histone deacetylase |
| HES | Hospital Episode Statistics |
| HHM | Hand-held myometry |
| HR | Hazard ratio |
| HRCU | |
| HRQoL | Health-related quality of life |
| HRG | Healthcare resource group |
| HST | Highly specialised technology |
| HTA | Health technology assessment |
| HTMF | Hand-to-mouth function |
| HUI | Health Utilities Index |
| ICER | Incremental cost-effectiveness ratio |
| ICF-CY | International Classification of Functioning, Disability, and Health – Children and Youth |
| IDMC | Independent data monitoring committee |
| IMP | Investigational medicinal product |
| IPD | Individual patient data |
| IQ | Intelligence quotients |
| IQR | Interquartile range |
| ITC | Indirect treatment comparison |
| ITT | Intention-to-treat |
| KM | Kaplan–Meier |
| LOA | Loss of ambulation |
| LS | Least squares |
| LY | Life year |
| LYG | Life years gained |
| MAIC | Matching-adjusted indirect comparison |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFF | Muscle fat fraction |
| MFM | Motor function measures |


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| | |
|---|---|
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MRI | Magnetic resonance imaging |
| MRS | Magnetic resonance spectroscopy |
| NHB | Net health benefit |
| NHSE | National Health Service England |
| NMB | Net monetary benefit |
| NHM | Natural history model |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIV | Non-invasive ventilation |
| NR | Not reported |
| NSAA | North Star Ambulatory Assessment |
| OLE | Open-label extension |
| OS | Overall survival |
| OTC | Over the counter |
| PAS | Patient access scheme |
| PCA | Prescription Cost Analysis |
| PedsQL | Pediatric Quality of Life Inventory |
| PEF | Peak expiratory flow |
| pFVC | Predicted forced vital capacity |
| PK | Pharmacokinetics |
| PODCI | Pediatric Outcomes Data |
| PPIE | Patient and Public Involvement and Engagement |
| PSA | Probabilistic sensitivity analysis |
| PSS | Personal social services |
| PSSRU | Personal Social Services Research Unit |
| PUL | Performance of upper limb |
| ONS | Office for National Statistics |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| QTcF | Fridericia-corrected QT interval |
| RCT | Randomised controlled trial |
| SAE | Serious adverse event |
| SAS | Safety analysis set |
| SD | Standard deviation |
| SE | Standard error |
| SF-36 | 36-item Short Form Health Survey |
| SLR | Systematic literature review |
| SMC | Scottish Medicines Consortium |
| SmPC | Summary of Product Characteristics |
| STA | Single technology appraisal |
| TFT | Timed function test |
| TLR | Targeted literature review |
| TSD | Technical Support Document |
| TTRF | Time to rise from the floor |
| UK | United Kingdom |
| US | United States |
| VL | Vastus lateralis |
| VAS | Visual analogue score |
| WTP | Willingness to pay |


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# B.1 Decision problem, description of the technology and clinical care pathway

## *B.1.1 Decision problem*

A summary of the decision problem is shown in Table 1.

The FDA marketing authorisation for givinostat is in boys and young men with Duchenne muscular dystrophy (DMD) aged ≥6 years, irrespective of whether they are still able to walk (i.e. are ambulant) or not;[1] the GB marketing authorisation is anticipated to specify the same patient population.

This submission covers a restricted population of boys and young men with DMD aged ≥6 years who are ambulant when they initiate givinostat treatment; this includes boys and young men who are ambulant when they initiate givinostat and become non-ambulant during treatment. This is narrower than the final NICE scope. The company is proposing a Patient access scheme (PAS) covering this restricted population; the PAS does not cover boys starting givinostat in the non-ambulant setting.

The Company understands the challenges of appraising the cost-effectiveness of therapies in DMD. In particular, that the prevalence of DMD means that it no longer meets the criteria for assessment under the Highly Specialised Appraisal (HST) route, which has been used for the only treatment previously recommended by NICE for DMD, ataluren. The Company believes that while NICE has determined the Single Technology Appraisal (STA) route as suitable for appraisal of givinostat, it is important for the clinical, economic and societal benefit of givinostat to be assessed in this complex challenging, paediatric, life-limiting, progressive disease.[2] This belief is supported by multiple external stakeholders, including Duchenne UK who believe that DMD treatments should be appraised by an HST route that can approach DMD with the pragmatism, sensitivity, and flexibility required.[2]

Finally, in contrast to the NICE scope, the Company does not consider ataluren an appropriate comparator for givinostat in this appraisal. The use of ataluren in routine clinical practice for people aged 2 years and older with DMD who have a mutation in the dystrophin gene, a small subgroup of the DMD population, is anticipated to decline following regulatory reappraisal in Europe, which has questioned efficacy within its license.[3–5] Having concluded that the totality of the evidence shows a negative benefit-risk balance, the European Medicines Agency (EMA) recommended in June 2024 that the marketing authorisation for ataluren should not be renewed.[6] The company is not aware of any information in the public domain about a reappraisal of ataluren by the Medicines and Healthcare Products Regulatory Agency (MHRA) but considers that given the significant uncertainty in terms of its efficacy, future access to ataluren, and therefore use as part of routine National Health Service (NHS) clinical practice for the treatment of DMD, is highly uncertain. Further, the NICE appraisal of ataluren followed the HST route.[7] Process differences between HST and STA evaluations prevent direct cost-effectiveness comparisons between givinostat and ataluren. Therefore, the company does not consider that ataluren should be included as a comparator to givinostat.


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**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | People with Duchenne muscular dystrophy 6 years of age and older | People with Duchenne muscular dystrophy 6 years of age and older who are ambulant when they initiate givinostat | The proposed population aligns with the Phase 3 EPIDYS trial for givinostat and is consistent with the available clinical data compared with current standard of care. Information on boys/young men who initiate givinostat when non-ambulant are anticipated to be available from the ULYSSES trial in late 2028 |
| **Intervention** | Givinostat | Givinostat | N/A |
| **Comparator(s)** | • ECM without givinostat<br>• Ataluren (for people aged 2 years and older with a nonsense mutation in the dystrophin gene and can walk [ambulatory]) | • ECM without givinostat | The company notes that the EMA confirmed the CHMP recommendation for non-renewal of the conditional marketing authorisation for ataluren for DMD in January 2024.[4] The CHMP made this recommendation after re-examining data from a study carried out after its conditional approval identified that treatment with ataluren "failed to show the medicine was effective in patients with a progressive decline in their ability to walk"[4]<br>Having concluded that the totality of the evidence shows a negative benefit-risk balance, in June 2024 the EMA recommended that the marketing authorisation for ataluren should not be renewed[6]<br>The company is not aware of any information in the public domain about a reappraisal of ataluren by the MHRA but considers that the use of ataluren as part of routine NHS clinical practice for the treatment of DMD may become uncertain during the course of the appraisal of givinostat<br>In addition, ataluren is only approved for use in a small subgroup of ambulatory patients who have a nonsense mutation in the dystrophin gene.[3] This accounts for approximately 10–15% of boys and young men with DMD.[5] Consequently, the NICE |


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| | | | |
|---|---|---|---|
| | | | appraisal of ataluren followed the HST route, and ataluren was therefore assessed against a different cost-effectiveness threshold, than the STA route for givinostat.[7] The company believes that should assessment of cost-effectiveness vs. ataluren be deemed necessary by NICE, then any appraisal should also be considered separately under the HST route |
| **Outcomes** | • Walking ability (ambulation)<br>• Muscle function<br>• Muscle strength<br>• Ability to undertake activities of daily living<br>• Bone function<br>• Cardiac function<br>• Concordance and optimisation of treatment<br>• Endocrine function<br>• Lung function<br>• Time in wheelchair<br>• Number of falls<br>• Time to scoliosis<br>• Lower body function<br>• Upper body function<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life (people with DMD and carers) | The company submission considers the following outcomes:<br>• Walking ability (ambulation)<br>• Muscle function<br>• Muscle strength<br>• Ability to undertake activities of daily living<br>• Cardiac function<br>• Concordance and optimisation of treatment<br>• Lung function<br>• Time to scoliosis<br>• Lower body function<br>• Upper body function<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life (people with DMD and carers) | Outcomes data relating to bone function, endocrine function, time in wheelchair, and number of falls are not included due to a lack of data |

Abbreviations: CHMP, Committee on Medicinal Products for Human Use; DMD, Duchenne muscular dystrophy; ECM, established clinical management; EMA, European Medicines Agency; HST, highly specialised technology; MHRA, Medicines and Healthcare Regulatory Agency; N/A, not applicable; STA, single technology appraisal.


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## *B.1.2 Description of the technology being appraised*

A description of givinostat is presented in Table 2. The draft Summary of product characteristics (SmPC) is provided in Appendix C.1. The United Kingdom (UK) public assessment report is not yet available.

**Table 2: Technology being appraised**

<table>
<tr><td>UK approved name and brand name</td><td>Givinostat (Duvyzat®)</td></tr>
<tr><td>Mechanism of action</td><td>Givinostat is a novel, orally administered, class I and II zinc-dependent histone deacetylase inhibitor (HDACi) that, by modulating aberrant gene expression and cell signalling in the muscle, restores muscle homeostasis and promotes muscle regeneration processes in patients affected by DMD. Givinostat reduces inflammation, fibre cell injury, intramuscular fibrosis and fatty replacement while promoting myogenesis in patients with DMD.[8, 9]<br><br>As an HDACi, givinostat can modulate histone and protein acetylation state, regulating gene expression and protein function, stability, and degradation. Hence, givinostat modulates aberrant gene expression and pathological intracellular and extracellular signalling in the muscle fibres and in the basal lamina, reducing inflammation and re-establishing the expression of proteins and miRNAs necessary to restore skeletal muscle homeostasis and re-activate myogenesis. As a result, givinostat mitigates the pathological downstream effects originated by the absence of dystrophin without correcting the primary genetic defect[9, 10]</td></tr>
<tr><td>Marketing authorisation/CE mark status</td><td>The Food and Drug Administration approved givinostat on 21 March 2024<br><br>A marketing authorisation application has been submitted to the MHRA through the International Recognition Procedure, with an anticipated approval in Q1 2025</td></tr>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics (SmPC)</td><td>Givinostat is indicated for the treatment of Duchenne muscular dystrophy in patients 6 years of age and older (FDA indication, and indication submitted to MHRA but not yet confirmed)</td></tr>
<tr><td>Method of administration and dosage</td><td>The recommended dosage of givinostat is based on body weight and administered twice daily with food
<table>
<tr><td>Actual body weight</td><td>Dosage</td><td>Oral suspension volume</td></tr>
<tr><td>10 kg to <20 kg</td><td>22.2 mg twice daily</td><td>2.5 mL twice daily</td></tr>
<tr><td>20 kg to <40 kg</td><td>31 mg twice daily</td><td>3.5 mL twice daily</td></tr>
<tr><td>40 kg to <60 kg</td><td>44.3 mg twice daily</td><td>5 mL twice daily</td></tr>
<tr><td>≥60 kg</td><td>53.2 mg twice daily</td><td>6 mL twice daily</td></tr>
</table>
In the givinostat clinical studies, the dose of givinostat was expressed as “givinostat hydrochloride monohydrate”, whereas the dose described in the draft SmPC is “givinostat” free base.<br>10 mg/mL givinostat hydrochloride monohydrate = 8.86 mg/mL givinostat</td></tr>
<tr><td>Additional tests or investigations</td><td>• Monitor blood counts every 2 weeks for the first 2 months of treatment, at Month 3 and then every 3 months thereafter</td></tr>
</table>


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| | |
|---|---|
| | • Monitor triglycerides at 1 month, 3 months, 6 months, and then every 6 months thereafter<br>• In patients with underlying cardiac disease or taking concomitant medications that cause QT prolongation, obtain electrocardiograms (ECGs) prior to initiating treatment with givinostat, during concomitant use, and as clinically indicated |
| **List price and average cost of a course of treatment** | Duvyzat (givinostat) 8.8 mg/ml oral suspension £13,846.00 per bottle (1 x 140 ml bottle).<br><br>The costs per monthly cycle based on this list price are:<br>• 10kg ≤ and < 12.5kg: £7,746<br>• 12.5kg ≤ and < 20kg: £12,726<br>• 20kg ≤ and < 25kg: £16,001<br>• 25kg ≤ and < 30kg: £17,262<br>• 30kg ≤ and < 40kg: £15,864<br>• 40kg ≤ and < 50kg: £19,003<br>• 50kg ≤ and < 60kg: £21,375<br>• 60kg ≤ and < 70kg: £23,297<br>• 70kg ≤: £27,199 |
| **Patient access scheme (if applicable)** | A patient access scheme (PAS) is pending approval from National Health Service England (NHSE); a simple discount of [redacted] is applied to the cost of givinostat – this reduces the price to £[redacted] per bottle. |

Abbreviations: DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; HDACi, histone deacetylase inhibitor.

Dystrophin is a structural protein linking the cytoskeleton of muscle fibres to the extracellular matrix through the dystrophin-associated protein complex (DAPC). It plays a crucial role in maintaining the structural integrity of the muscle cell fibre membrane (sarcolemma).

DMD is caused by mutations in the dystrophin gene, resulting in an absence or non-functional dystrophin.[11] The sequence of pathological events resulting from the absence of dystrophin and the consequent hyperactivation of histone deacetylase (HDAC) comprises muscle fibre injury, the activation of chronic inflammatory pathways, the impairment of muscle regeneration mechanisms, and fibrogenesis and adipogenesis.[12–15] In simple terms, too much HDAC enzyme activity in DMD, means that too many acetyl groups are removed from the histones and that the DNA is too tightly wrapped, which prevents expression of genes and failure to produce specific proteins.[16] Specifically for muscle damage repair this means the immune response gets 'out of control', and fibro-adipogenic stem cells get stuck in connective tissue production mode and become fibroblasts and fat cells, instead of supporting the muscle stem cells to differentiate and repair muscle. Furthermore, muscle stem cells can not differentiate and can no longer repair muscle. In addition to histones, other proteins are also regulated by the addition and removal of acetyl groups, which can further exacerbate muscle damage and pathology in DMD.[16]

The inhibition of HDAC hyperacetylation re-establishes the expression of proteins in muscle cells from boys and young men with DMD and miRNAs essential for restoring skeletal muscle homeostasis and activating muscle stem cells, to improve muscle repair.[15, 16]

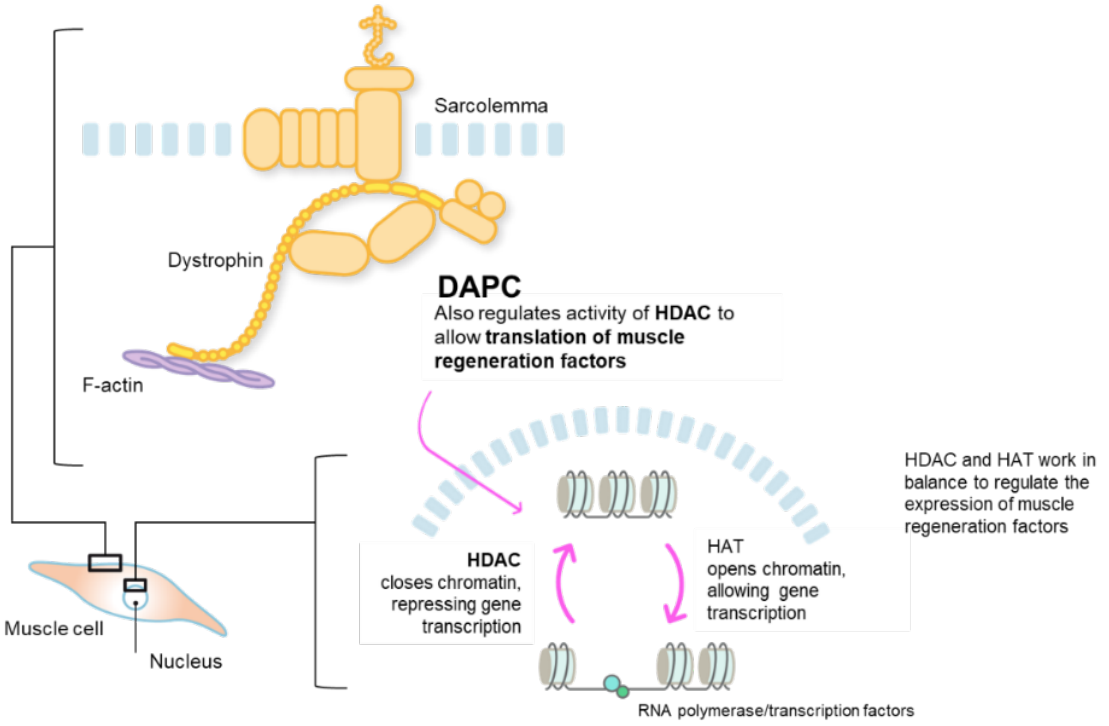
Givinostat is a pan-HDAC inhibitor that counteracts the pathogenic events downstream of dystrophin deficiency (Figure 1). In a mouse DMD model, givinostat increased cross-


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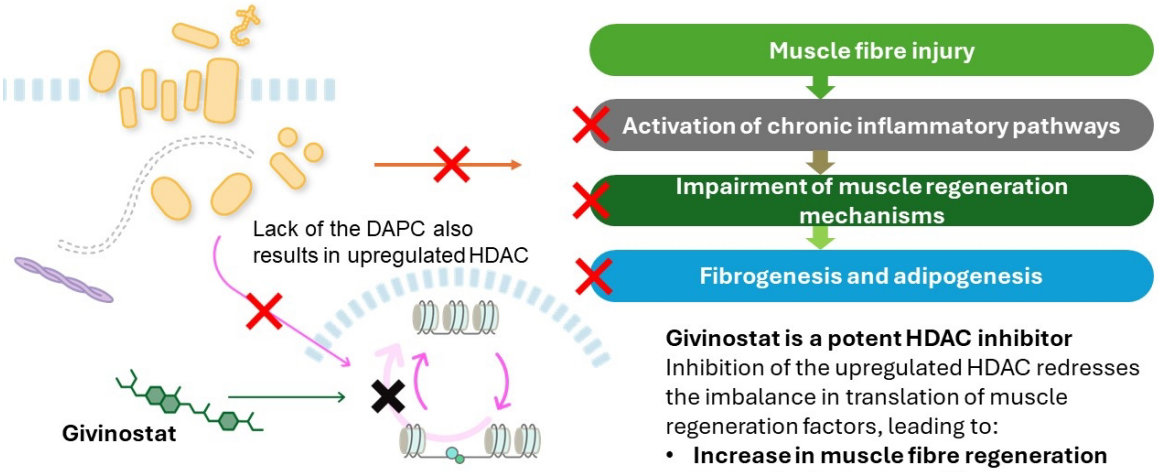
sectional myofibre area and decreased inflammatory infiltrate and fibrotic scars,[17] and, in a Phase 2 study, increased muscle fraction and reduced tissue fibrosis, necrosis and fatty replacement in brachial biceps biopsies.[18] Givinostat is anticipated to provide benefits regardless of age or underlying DMD mutations and there is no clinical rationale for expecting its efficacy to be different in muscles used for walking versus other muscles in the body, such as those involved in hand to mouth function, respiration and cardiac function.[19, 20]


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**Figure 1: Givinostat mechanism of action**




HDAC inhibition also leads to reduced activation of immune cells with a **reduction in pro-inflammatory cytokine release**, and reduced fibroblast activation with a **reduction in fibrosis**




**Givinostat is a potent HDAC inhibitor**
Inhibition of the upregulated HDAC redresses the imbalance in translation of muscle regeneration factors, leading to:

- **Increase in muscle fibre regeneration**
- **Reduction in fat deposition**
- **Delayed disease progression with preservation of functional capabilities**

Abbreviations: DAPC: Dystrophin-associated Protein Complex; HAT: Histone acetyltransferases; HDAC: Histone deacetylase; HDACi: Histone deacetylase inhibitor.
Source: Consalvi S, et al. 2011;[12] Kodippili K, Rudnicki MA. 2023;[21] Mercuri E, et al. 2024;[22] ClinicalTrials.gov. Available at https://clinicaltrials.gov/study/NCT02851797;[23] Bettica P, et al. 2016 (suppl);[24] Wilson DGS, et al. 2022;[25] Campbell KP, Kahl SD. 1989;[26] Giraud S, et al. 2015;[27] Reid AL, Alexander MS. 2021;[28] Ervasti JM, Campbell KP. 1993.[29]


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## *B.1.3 Health condition and position of the technology in the treatment pathway*

**DMD is a rare, progressive, lethal neuromuscular disorder that typically affects boys due to its X-linked hereditary pattern.**[30]

**Dystrophin is an important cytoskeletal protein that supports the strength, stability, and functionality of muscle cells and is coded for by the dystrophin gene.**[13]

- The absence of dystrophin and the consequent hyperactivation of HDAC results in a sequence of pathological events comprising muscle fibre injury, the activation of chronic inflammatory pathways, the impairment of muscle regeneration mechanisms, and fibrogenesis and adipogenesis.[10, 12–14]

**DMD is a rare disease. In the UK, approximately 100 boys are born each year who will be diagnosed with DMD,**[31] **and around 529 boys with DMD aged ≥6 years who are able to walk are estimated to be living with the condition in the UK at any one time.**[32]

**DMD is characterised by concurrent, progressive injury of all muscles throughout the whole body starting at birth. Key milestones of disease progression are the loss of ambulation and the loss of upper limb function, including fine motor control.**[33]

- Impairment in lower limb function is usually the first symptom to be noticed at between three and five years of age. As patients age, muscular damage accumulates throughout the body, increasing symptom severity levels and lowered function scores.[33, 34]
- Loss of ambulation and wheelchair dependency typically occurs around 12 years of age.[35] Around the time of loss of ambulation, upper limb function also starts to deteriorate, with loss of both shoulder elevation and hand-to-mouth activity from the mid-teens.[33]

**The median survival of boys and young men with DMD is 22–28 years**[36–40]

- Respiratory muscle function decline requires partial and then full-time ventilation assistance and possibly tracheostomy.[41] DMD is also associated with dilated cardiomyopathy that contributes to heart failure and arrhythmias.[42]
- Cardiovascular and respiratory complications are the leading causes of morbidity, unplanned hospital admissions and mortality in boys and young men with DMD.[43, 44]

**Delaying loss of ambulation and upper limb function is a critical outcome as these are the key milestones of disease progression that have the most significant detrimental effect on health-related quality of life (HRQoL) in boys and young men with DMD and their caregivers**

- Adolescence is usually a time of growing independence and autonomy, but boys and young men with DMD will need their parents to provide increasing help with activities of daily living (ADLs), including intimate and personal care, as their functional abilities continuously decline.[45]
- Compared to boys and young men with DMD who still retain physical independence, wheelchair dependence, loss of upper limb function, and the ability to swallow negatively impact HRQoL,[34] emphasising the substantial impact of disease progression on patients' well-being.
- Loss of hand function prevents participation in most daily activities of adolescence, such as driving an electric wheelchair, eating, schoolwork, computer games and interacting with others on social media and is often considered more difficult than the transition to requiring a wheelchair.[46, 47]
- Lower levels of strength and slower rates of functional performance correlate with participation in fewer physical and social activities.[48–50]

**Caregiver burden increases with disease progression, significantly impacting their overall quality of life (QoL) and physical, emotional, and mental well-being.**

- Caregivers of boys and young men with DMD frequently experience anxiety, depression, and impaired mental health,[51, 52] as well as physical health issues due to the physically demanding nature of caring for a child/young adult with DMD.
- Caregivers face constraints and hidden costs that impact their health and financial well-being long beyond the usual period of childhood dependency.[53]


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- Grief is an inseparable aspect of parenting a child or young adult with DMD.[51] Although at its most intense at the time of death of their child, parents experience grief before bereavement and at each disease progression point, such as loss of ambulation, requirement for enteral feeding, and need for non-invasive ventilation.[51]

**The impact of DMD extends beyond the person with DMD and their parents to siblings, grandparents, the wider family and the local community.**

- Caring for boys and young men with DMD is time-consuming and complex. It requires multiple caregivers, e.g. both parents, siblings, grandparents, or members of the wider family, alongside the multidisciplinary healthcare team.
- The childhood of siblings without DMD is also significantly affected. Early caregiving can lead to practical and psychological difficulties for the sibling, negatively impacting their social life and emotional well-being.[28]
- The most significant changes in a child's physical ability will occur during their school years. Specialist support and modifications to the classroom environment to address their additional learning and behavioural needs are necessary to enable children with DMD to reach their potential.[1, 54]

**The management of boys and young men with DMD imposes a substantial direct cost on healthcare systems, which increases with disease progression.**

- The average cost associated with the care and treatment of boys and young men with DMD was estimated to be ten times higher than that of the cost incurred by the overall population.[55]
- Rehabilitation services (e.g. physiotherapy, occupational therapy, and speech and language therapy) and medical aid costs were shown to represent the main drivers for direct medical costs, accounting for 50% of the direct annual costs of DMD.[56]
- Costs increased when patients became full-time wheelchair users and required respiratory support.[56, 57]

**DMD management requires a multidisciplinary approach to optimise the primary manifestations and secondary complications of the disease**

- DMD is a complex, multisystem disease managed by a multidisciplinary team for which there is no cure. The goal of treatment is to allow boys and young men with DMD to experience as much of childhood as possible by slowing the progressive trajectory of muscle loss thereby maintaining independence and delaying the time to loss of ambulation and loss of upper limb function
- Established clinical management (ECM) for boys with DMD in England and Wales includes physiotherapy, corticosteroids (CS) and other supportive care.

**There is a high unmet need for a new therapy for boys and young men with DMD that demonstrates a clinically meaningful and statistically significant improvement in functional endpoints compared with the current standard of care regardless of specific dystrophin gene mutation type.**

### B.1.3.1 Disease overview

#### Disease description

DMD is a rare, progressive, lethal neuromuscular disorder which almost exclusively affects boys due to its X-linked recessive genetic pattern.[30] Cases of DMD in girls are extremely rare, with an estimated rate of 1 case per 50 million births.[58]

Dystrophin is an important cytoskeletal protein that supports the strength, stability, and functionality of muscle cells and is coded for by the dystrophin gene.[13] Dystrophin is expressed at the plasma membrane of all muscles, including cardiac, smooth, and skeletal muscle, as well as some neurons.[59] The dystrophin gene is the largest known human gene, covering 2.4 megabases (0.08% of the human genome) at locus Xp21.[60] Consequently, compared with other human genes, the dystrophin gene has a high mutation rate, with over


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7,000 different dystrophin mutations identified.[61–64] Deletions and duplications, the most common forms of DMD mutations, typically disrupt the translational reading frame of the gene, resulting in an absence of functional dystrophin proteins.[61–65] One-third of dystrophin gene mutations occur *de novo*, while the remaining two-thirds are inherited from a carrier mother or result from germline mosaicism.[65, 66]

### Role of dystrophin in DMD

Dystrophin is a structural protein within the muscle fibre cell that links the cytoskeleton of muscle fibres to the extracellular matrix through the DAPC. Dystrophin plays a crucial role in maintaining the integrity of the sarcolemma, working as a shock absorber to prevent its rupture during muscle contraction.[12, 27, 28] The absence of dystrophin and the consequent hyperactivation of HDAC results in a sequence of pathological events comprising muscle fibre injury, the activation of chronic inflammatory pathways, the impairment of muscle regeneration mechanisms, and fibrogenesis and adipogenesis.[10, 12–14]

### Impact of DMD on children, caregivers, family members and the wider community

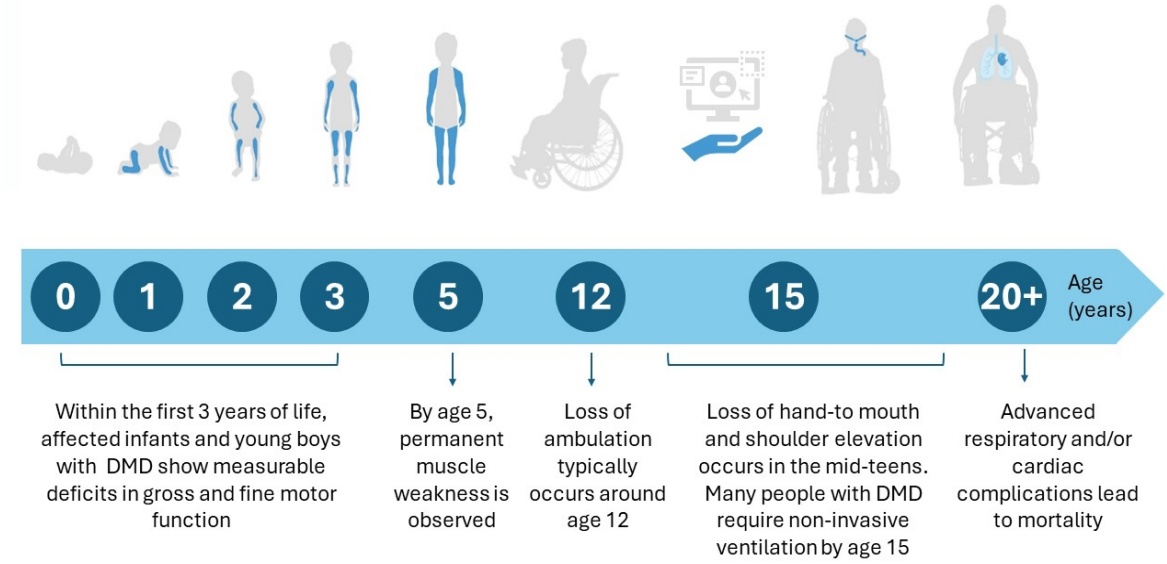
DMD is characterised by progressive injury of all muscles throughout the body, starting at birth. Symptoms are usually first noticed between three and five years of age, although in some cases, they can present in children as young as two and are typically observed as missed gross motor milestones, ultimately resulting in the loss of ambulation, then continuing with disease progression to result in impairment, then loss of upper limb function, wheelchair dependency, and premature death.[33] The life expectancy of boys and young men with DMD is 22–28 years.[36–40] The diagnosis of DMD is devastating for a family, and there is often very little psychological support for them to come to terms with it, or the complex grief that occurs after bereavement. Furthermore, given the heritability of dystrophin gene mutations from carrier mothers, some families may have two or more children with DMD.

> **"The doctor said my son, 3, wouldn't live beyond 20. My world fell apart…no counselling, no support. Just a simple message to prepare for life with a seriously disabled child and try and make the most of it."**
>
> *Parent of a son with DMD.*[67]

Around the time of wheelchair dependence, commonly 12 years of age,[11] boys and young men with DMD experience a rapid progression of muscular contractures and scoliosis. Scoliosis specifically has a detrimental impact on chest cavity size and positioning, leading to respiratory issues that require surgery.[68] Alongside this, continued muscle weakening, particularly of the intercostal muscles and diaphragm, increases the need for cough and ventilatory support.[34, 35] DMD is also associated with dilated cardiomyopathy that contributes to heart failure and arrhythmias.[42] Cardiovascular and respiratory complications are the leading causes of morbidity, unplanned hospital admissions and mortality in boys and young men with DMD (Figure 2).[43, 44]


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**Figure 2: DMD progression milestones**




Abbreviations: DMD, Duchenne muscular dystrophy.
Source: Adapted from Walter and Reilich, 2017[33]

Lower levels of strength and slower rates of functional performance correlate with participation in fewer physical and social activities.[48–50] Compared to boys and young men with DMD who still retain physical independence, wheelchair dependence, loss of upper limb function, and the ability to swallow negatively impact HRQoL. Loss of upper limb and hand function is enormously impactful as it prevents participation in most daily activities of adolescence, such as driving an electric wheelchair, eating, schoolwork, computer games and interacting with others on social media and is often considered more difficult than the transition to requiring a wheelchair.[46, 47] Disease progression also significantly affects caregivers' - primarily the child's parents - overall QoL, physical, emotional, and mental well-being, social connections, and employment status.[45, 56, 69, 70] However, the impact of DMD extends beyond the person with DMD and their parents to siblings, grandparents, the wider family, and the local community. The most significant changes in a child's physical ability occur during their school years. As well as the adaptations required at home, the presence of additional physical, behavioural, and learning needs requires local authority funding for specialist support and adaptations to the classroom environment to ensure children with DMD can reach their potential.[1, 54]

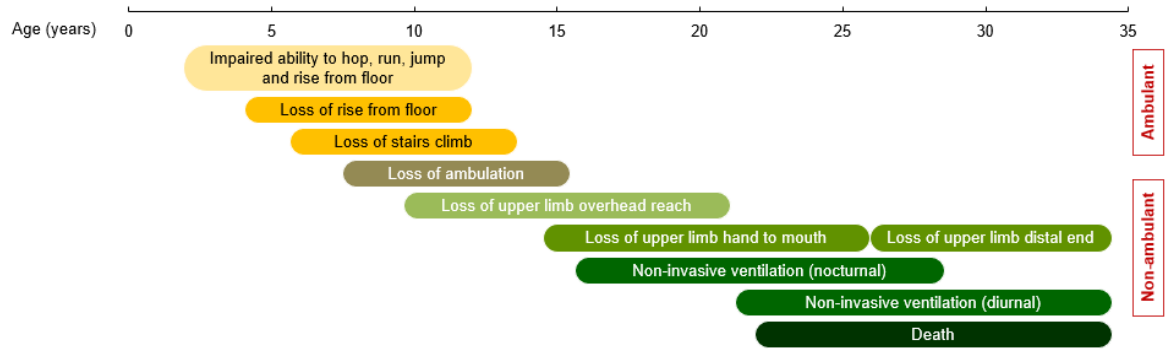
### B.1.3.2 Progression and disease course

Children with DMD show clinical heterogeneity, leading to considerable variability in the rate of disease progression,[71] however, in all cases, DMD is linked to severe outcomes and reduced life expectancy.[36–40] While concurrent, progressive muscle injury of all muscles starts at birth, during the natural course of the disease, impairment of lower limb function is typically observed first and as patients age, muscular damage accumulates, leading to increasing symptom severity and lowered function scores.[33, 34] Initially, boys and young men


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with DMD experience sequential loss of important early developmental milestones, including difficulties getting up from the floor, standing, walking, and climbing stairs.[34, 35] These difficulties contribute to frequent falls and a considerable risk of bone fractures. [11, 30, 71, 72] The decline in lower limb function becomes apparent in the initial decade of life, ultimately leading to loss of ambulation and wheelchair dependency in the early teens (Figure 3).[35]

**Figure 3: Consequences of DMD disease progression**




Abbreviations: DMD, Duchenne muscular dystrophy.
Source: Adapted from Walter and Reilich, 2017[33]

Around the time of loss of ambulation, upper limb function also starts to deteriorate, with loss of shoulder elevation and hand-to-mouth activity occurring from the mid-teens.[33] As a consequence of increasing upper limb muscle weakness, boys and young men with DMD experience a deterioration in their hand skills, which follows from decreased joint mobility and contractures in the wrist and fingers.[46] This prevents them from using, for example, computers and smartphones, that would otherwise provide virtual access to their friends, hobbies and interests and overcome any social isolation resulting from their physical disability.

The primary cause of pulmonary function decline in DMD is respiratory insufficiency related to respiratory muscle failure, typically diagnosed in adolescence.[33] The pattern of pulmonary decline begins with volume decline, followed by weak cough, hypoventilation requiring partial and then full-time ventilation assistance, and possibly tracheostomy if non-invasive techniques fail or other support and illness factors predict the need.[41] In a retrospective longitudinal cohort study estimating mortality rates and survival probabilities in the UK DMD population through Clinical Practice Research Datalink (CPRD) records, the median age of ventilation support was 16.97 years.[37]

Pathogenic changes in the cardiac muscle begin at an early age for DMD, and clinically significant dysfunction is typically seen during the second decade. Most individuals with DMD will eventually have dilated cardiomyopathy,[41] with a mean age of onset at approximately 15.26 years.[37] Those with severe cardiomyopathy will typically die from cardiac-related causes and are unable to qualify for transplant surgery due to skeletal muscle impairment, rejection, and low levels of pulmonary function.


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### B.1.3.3 Staging/classification of DMD

DMD can be classified into five stages according to the appearance and progression of symptoms, with loss of ambulation being a key early progression milestone (Table 3).[11] Loss of ambulation generally occurs around the age of 12 years; the estimated median age at loss of ambulation in a 2022 analysis of data from the UK North Star Network database was 11 years 8 months (interquartile range: 10 years 1 month–14 years 5 months).[73]

**Table 3: DMD disease symptoms and milestones**

| Disease Stage | Age | Identifying Symptoms and Disease Milestone |
|---|---|---|
| Pre-symptomatic | 1 to 3 years old | First symptoms of development delay including delayed walking, frequent falls, and difficulty with running and climbing stairs<br>Bulky calf, pelvis, and thigh muscles<br>Gait disturbance not yet apparent |
| Early Ambulatory | 4 to 7 years old | Gower's sign, waddling gait, toe walking<br>Ability to climb stairs is retained |
| Late Ambulatory | 8 to 11 years old | Progressively laboured gait<br>Loss of ability to climb stairs and rise from the floor<br>Still able to walk 10 metres without assistance |
| Early Non-Ambulatory | 12 to 19 years old | No longer able to walk 10 metres without assistance<br>Transition to requiring a wheelchair to aid mobility<br>Ability to self-propel and maintain posture is retained for a period<br>Development of scoliosis and muscular contractures<br>Increased risk of respiratory complications and onset of cardiomyopathy<br>May require night-time ventilation |
| Late Non-Ambulatory | >19 years old | Pronounced limitations<br>Increasingly limited upper limb function and postural maintenance<br>Loss of hand-to-mouth function<br>Requires night-time ventilation or full ventilation |

Abbreviations: DMD, Duchenne muscular dystrophy.
Source: Bello, 2016;[74] Bushby; 2010a;[75] Ryder, 2017,[30] North Star, 2024.[76]

### B.1.3.4 Epidemiology

DMD is one of the most severe and common forms of childhood muscular dystrophy, with a worldwide birth incidence of around 1 in 5,050 boys.[77] In the UK, approximately 100 boys are born each year who will be diagnosed with DMD.[31] The total population eligible for treatment with givinostat is estimated to be 529 in Year one, rising to 901 patients in Year five, based on data sourced from the NorthStar UK data.[32]

### B.1.3.5 Diagnosis

Ensuring a timely and accurate diagnosis of DMD is crucial for effective management, allowing early intervention and appropriate genetic counselling. A dystrophinopathy should be suspected in patients with symptoms of weakness, characteristic physical exam, and a possible family history of the disease.[78] Laboratory testing involves creatinine kinase


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measurements, muscle biopsies, gene testing, and electrocardiogram (ECG) findings for cardiomyopathy. Diagnosis should be conducted by a neuromuscular specialist who can clinically evaluate the patient and efficiently obtain and interpret the diagnostic tests in the context of the clinical presentation.[11, 79] Following a DMD diagnosis, carrier testing and genetic counselling are essential.[11]

### B.1.3.6 Burden of DMD

In September 2024 Duchenne UK published their State of the Nation report that highlighted the considerable gaps in DMD treatment, care and support.[2] They reported that two families a week are given the devastating diagnosis that their child has DMD and described the huge impact that the disease has on boys/young men living with it and on those who love and care for them. Duchenne UK state that in addition to physical disabilities, boys and young men with the disease commonly experience high levels of anxiety, anger, and sleeping problems leading to extreme tiredness. The impact of these difficulties was reported to be evident in the family's quality of life, specifically affecting the mental health of the parents, relationships with siblings and family outings. This  pain and struggle goes largely unnoticed by most of the UK, mainly because DMD is a rare disease.[2]

#### Mortality and prognosis

Data from the UK suggests that life expectancy for boys and young men with DMD is in the range 22–28 years (Table 4).[36–40] This life expectancy estimate has been confirmed by clinicians in England and Wales at two advisory boards conducted by the company, who confirmed that this range reflects their experience in clinical practice, although some young men live for longer, but this is unusual.[19, 20]


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**Table 4: UK DMD mortality estimates**

| Author | Study design | Life expectancy (years) | |
|---|---|---|---|
| ITF Pharma UK. (2024) | Analysis of Hospital Episode Statistics data (n=1,937) | 28 | Males with DMD in the UK who died in inpatient spells or were discharged to a hospice (n=116) |
| | | 23 | Patients who had no health records in the past two years and were presumed to have died (n=40) |
| Broomfield, J (2023) | Natural history study using Clinical Practice Research Datalink (n=1,121) | 25.64 (95% CI 24.73 to 26.47) | The entire cohort |
| | | 26.47 (95% CI; 25.16 to 27.89) | A subgroup born after 1990 |
| Nart, L (2024) | Single centre retrospective cohort review (n=37) | 22.25 | Adults with DMD who died between 2011 and 2022 |
| Pietrusz, A (2023) | Multicentre, retrospective case note review (n=209) | 28.25 | Patients who were corticosteroid naïve (had taken CS for a total of 12 months or less) |
| | | 25.58 | Patients who had stopped corticosteroids |
| | | 28.83 | Patients who continued on corticosteroid treatment |
| Broomfield, (2021) | Systematic review of the published literature on mortality in DMD up to July 2020 (n=2,283). The review identified 18 studies, of which 3 included UK patients | 22.0 (95% CI; 21.2 to 22.4) | The entire cohort |
| | | 28.1 (95% CI 25.1 to 30.3) | A subgroup born after 1990 |

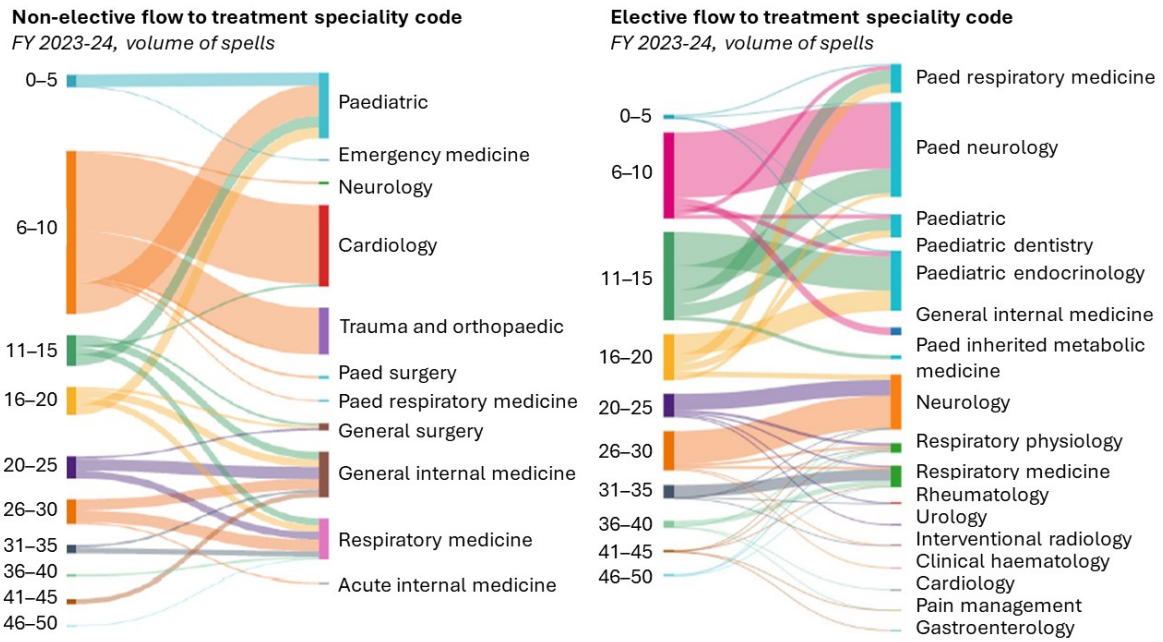
Abbreviations: CS, corticosteroids; DMD, Duchenne muscular dystrophy, UK, United Kingdom
Source: Data on file ITF Pharma UK;[36] Broomfield (2023);[37] Nart (2024);[39] Pietrusz (2023);[40] Broomfield (2021).[38]

### Clinical burden

Boys and young men with DMD and their families require support from a multidisciplinary team of experts in neurology, endocrinology, cardiac, emergency care, psychosocial, nutrition, orthopaedics, physiotherapy, and respiratory specialities (Figure 4).[80] In addition to progressive muscle weakness and loss of function, DMD complications include orthopaedic complications, cardiac complications, and respiratory complications.


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**Figure 4: Inpatient activity for children and adults**




Abbreviations: FY, financial year; Paed, paediatric.
Source: Data on file ITF Pharma UK (2024).[36]

*Orthopaedic complications*

Boys and young men with DMD may develop joint contractures, scoliosis, and fractures resulting from osteoporosis (Figure 5). The causes of these musculoskeletal complications are multifactorial, involving direct impact on the muscles from the disease itself, secondary effects from weakened muscles, and the related adverse events (AEs) of treatments, such as corticosteroid use, which affects bone strength.[81] Boys and young men with DMD have a lower bone and muscle mass, a higher fraction of fat mass versus muscle, and a higher likelihood of experiencing fractures due to fragility compared with boys and young men without the condition. This can be attributed to limited mobility, loss of muscle mass, and the prolonged use of CS.[81–83]


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**Figure 5: Young adult with DMD with scoliosis and contractures of the elbow, wrist, finger, hip, knee and ankle joints**



Images reproduced with permission from publisher.
Abbreviations: DMD, Duchenne muscular dystrophy.
Source: Marcelo (2023).[84]

Approximately 20% to 60% of boys and young men with DMD have low-trauma extremity fractures (typically the distal femur, tibia, or fibula), while up to 30% develop symptomatic vertebral fractures. If left untreated, these vertebral fractures can result in chronic back pain and spine deformity. Simultaneously, fractures in the legs can cause a premature, permanent loss of ambulation.[43]

*Respiratory complications*

Respiratory weakness in DMD is inevitable but usually becomes clinically relevant after loss of ambulation and strongly correlates with the progression of upper limb weakness.[44] The impact of DMD on respiratory function is largely a result of intercostal and diaphragm muscle weakness.[44] Boys and young men with DMD experience respiratory muscle fatigue, which leads to a decline in vital capacity and the development of stiff, non-compliant chest walls and lung volume restriction.[43] Mean annual decline for forced vital capacity (FVC) %-predicted was 5.6% (standard error: 2.1%) percentage points before loss of ambulation and 10.1% (2.2%) after loss of ambulation.[85] During the non-ambulatory stage, boys and young men with DMD develop weak cough efforts, placing them at risk of mucus plugging, atelectasis, pneumonia, ventilation-perfusion mismatch, and a heightened risk of progressing to respiratory failure, especially during respiratory tract infections.[43]

Ventilatory support is frequently required at this stage of the disease—initially overnight, but later, it may be needed 24 hours/day.[44] Non-invasive ventilation is considered in the first instance, but tracheostomy may be required during periods of acute illness.[44] Patients are at risk of severe dyspnoea, extended hospital admissions due to atelectasis or pneumonia, and fatal outcomes due to respiratory arrest or respiratory-induced cardiac arrhythmias.[43]


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Maintaining respiratory health is vital to prolonging survival and QoL in DMD.[44] Ventilatory support improves life expectancy. A systematic review showed that the median survival age in patients not receiving ventilatory support was between 14 and 27 years old, increasing with ventilatory support to between 21 and 39 years old.[48, 86]

Boys and young men with DMD may be at risk of undernutrition/malnutrition and being overweight or obese at different ages and under different circumstances, in addition to deficiencies in calories, protein, vitamins, minerals, and fluid intake. In the later stages of DMD, pharyngeal weakness leads to dysphagia, resulting in poor oral food intake. When combined with poor respiratory function, this can result in severe weight loss and the need to consider tube feeding.[11]

*Cardiac complications*

The absence of dystrophin in the cardiomyocytes increases cardiomyocyte structural vulnerability, membrane instability, disruption in Ca2+ homeostasis, elevated production of reactive oxygen species, and mitochondrial dysfunction. Dystrophin is also expressed in endothelial cells, vascular smooth muscle cells, and fibroblasts.[43, 87] As a result, boys and young men with DMD develop dilated cardiomyopathy, electrical conduction and ECG abnormalities such as atrial and ventricular tachycardias and atrial arrhythmias.[43, 87] Left ventricular dysfunction, dilation, and fibrosis, leading to end-stage heart failure, typically occur during the late teens.[87]

**Impact of the disease on boys with DMD**

Limited data describe the experiences of boys and young men with DMD, particularly during the non-ambulatory stage. However, a qualitative study of forty-six patient/caregiver dyads, including non-ambulatory patients, aimed to capture the lived experience of the disease.[88]

*Losing lower limb function*

Study participants described the most bothersome challenges of living with DMD as the mobility restrictions they experienced, as well as the emotional and social impacts that resulted from their physical function limitations. All ambulatory dyads (n=28, 100%) reported difficulties with weakness or lack of strength, and most reported tiring easily or lacking energy (n=24, 86%). Almost all ambulatory dyads reported at least one difficulty with mobility, including going up and down stairs (n=16, 57%), running (n=13, 46%), and walking (n=9, 32%). Approximately half of the ambulatory dyads reported the inability to keep up physically with their peers (n=15, 54%) and/or mobility restrictions (n = 14, 50%). These challenges impacted their ability to engage in activities they want to do, such as participation with their peers and negatively impacted their mood**. "I would say his physical ability to be outdoors and play with other kids [is negatively impacted]. He can't really play with other kids as I know he would like"**

Similarly, among the non-ambulatory dyads, lack of mobility (n=10, 56%) and inability to keep up with peers (n=5, 28%) were reported to be the biggest challenges, which often resulted in negative emotions and feeling different from peers and limited their ability to participate in social activities, play, and sports. One non-ambulatory individual indicated that he wanted to be **"Able to walk or just [have] a sense of normalcy. I want to be like my brothers, walking, running, playing sports."**


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*Losing upper limb function*

The loss of upper limb function leads to severe problems in performing daily activities and participating in society, ultimately affecting independence and QoL.[89] While the use of a wheelchair could facilitate independence, loss of upper limb function is more often framed as a source of ongoing frustration due to a steady decline in the ability to carry out self-care and leisure activities independently.[47] Adolescence is usually a time of growing independence and autonomy, but for boys and young men with DMD, their parents will need to provide increasing assistance with intimate and personal care (e.g. dressing, eating, washing and toileting).[45]

In the patient burden study, symptoms and impacts associated with impaired upper body function included difficulties with reaching for objects (n=14, 78%), fine motor skills such as holding a pencil or turning pages in a book (n=11, 61%), lifting arms above the head (n=10, 56%), and lifting objects (n=8, 44%), which resulted in patients needing additional assistance from caregivers or adaptive devices. Limitations in upper body function resulted in all non-ambulatory participants needing assistance with at least one ADL, including getting dressed (n=15, 83%), bathing (n=12, 67%), toileting (n=8, 44%), and eating and drinking (n=7, 39%). Most non-ambulatory participants reported needing help with transfers, such as getting in and out of bed (n=13, 72%), getting in and out of chairs (n=10, 56%), and being positioned when in bed (n=10, 56%), which further limited their independence. As a result of needing caregivers to reposition them during the night, most non-ambulatory dyads also described sleep problems and fatigue (both n=14, 78%).

**"Losing strength in my arms has limited my independence more than my legs. I find it much harder to do things for myself and it upsets me"**

*Patient aged 20 with DMD.*[90]

*Impact on childhood/adolescent experiences and participation*

The assessment of the ability of boys and young men with DMD to manage real-life situations, as outlined by the International Classification of Functioning, Disability, and Health-Children and Youth Version (ICF-CY) endorsed by the World Health Organization, emphasises the significance of participation as a crucial health outcome. In this context, participation is defined as direct engagement in various life activities, encompassing personal care, mobility, social relationships, education, recreation, spirituality, and community life.[91]

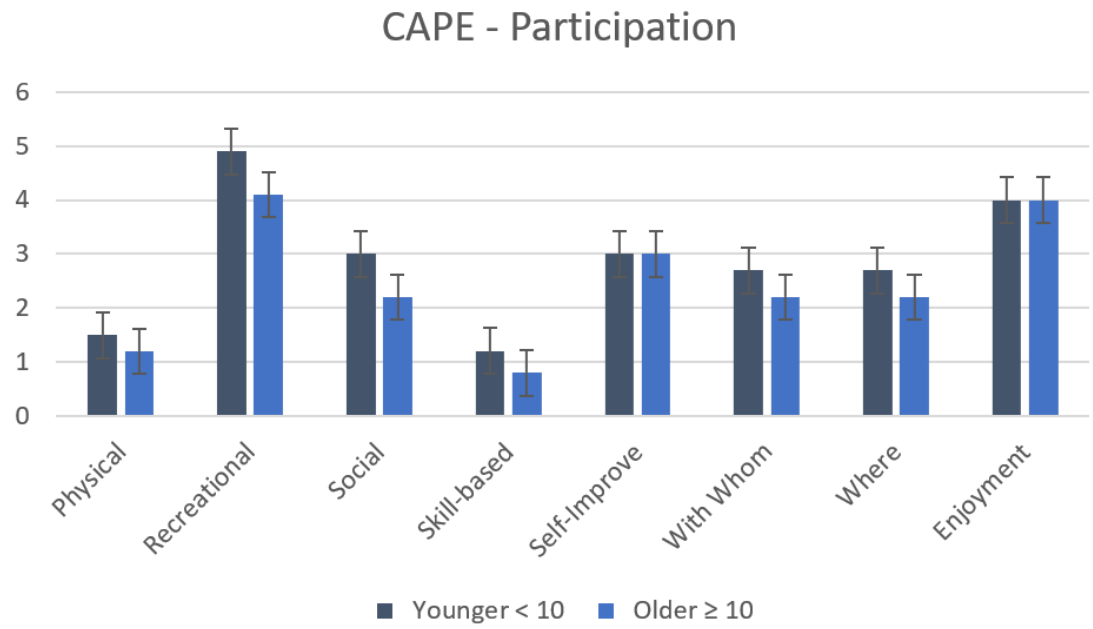
Related cross-sectional studies were conducted in boys and young men with DMD and age-matched unaffected controls to investigate how impairment arising from DMD affects their real-life experiences. The studies focused on participation in physical and social activities using the Children's Assessment of Participation and Enjoyment (CAPE).[50, 91] Self-reported assessments of participation were completed by participants with DMD with the assistance of their parent(s). The CAPE examines how children and youth participate in everyday activities. Scores on the CAPE are divided into five dimensions: 1) **Diversity**, the number of activities performed overall; 2) **Intensity**, the frequency of performing the activity; 3) **With Whom** the activity is performed; 4) **Where** the activity is performed; and 5) how


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much **Enjoyment** the child gets from the activity. Additionally, activities are divided into the following domains: physical, recreational, social, skill-based, and self-improvement. Physical activities include playing team sports, bicycling, and actively using playground equipment. Recreational activities include reading, playing cards or playing video/computer games. Social activities include visiting friends, going to the movies, and cooking.[50, 91]

In the earlier study, compared to age-matched unaffected controls, participation in physical activities was significantly lower in boys with DMD than in unaffected controls. The later study revealed a substantial reduction in the levels of participation in life activities among older boys and young men with DMD (10 years old and above) compared with the younger cohort (under ten years old). This decline in participation was most pronounced in recreational, social, and skill-based activities (Figure 6).[50, 91]

**Figure 6: CAPE scores in participation of everyday activities for younger and older children with DMD**




Abbreviations: CAPE: Children's Assessment of Participation and Enjoyment,.
Source: Bendixen, 2014.[50]

Social closeness with peers with similar life experiences can enhance the physical and psychological well-being of young men with DMD.[92] In a qualitative study of the psychosocial impacts of living with DMD, it appeared that social inclusion was particularly lacking during the transition into adulthood. Some young men with DMD described a narrowing of social opportunities and insufficient social supports to meet their changing needs. Participants related how social opportunities were limited because friends establish working lifestyles in which they are unable to readily fit. While some degree of social engagement may be maintained through online connections like multiplayer video games, disease progression was associated with social isolation.[47]


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*Transition between paediatric and adult services*

As children with DMD can be diagnosed as early as two years of age and live until their mid-20s, there is a necessary transition of care from paediatric to adult services over the individuals' life course. However, because of their highly complex healthcare needs that require the coordinated support of many different specialists, this transition of care can be difficult and can occur in a piecemeal fashion for boys and young men with DMD and, therefore, must be planned carefully.[93] In their report on transitions from children's to adult services, the Care Quality Commission described the experience of a young man with DMD who had transferred from the children's hospital at 16, the community children's team at 18 but remained with the children's specialist ventilation service because no comparable adult service existed in his area.[94] The variable coordination of transition contributes to confusion and distress for young people and families as a result of the lack of information, support, and services available to meet their complex health needs.[94] Further, inadequately planned transition processes could lead to negative outcomes related to mortality, prognosis, psychosocial and educational well-being.[92, 93]

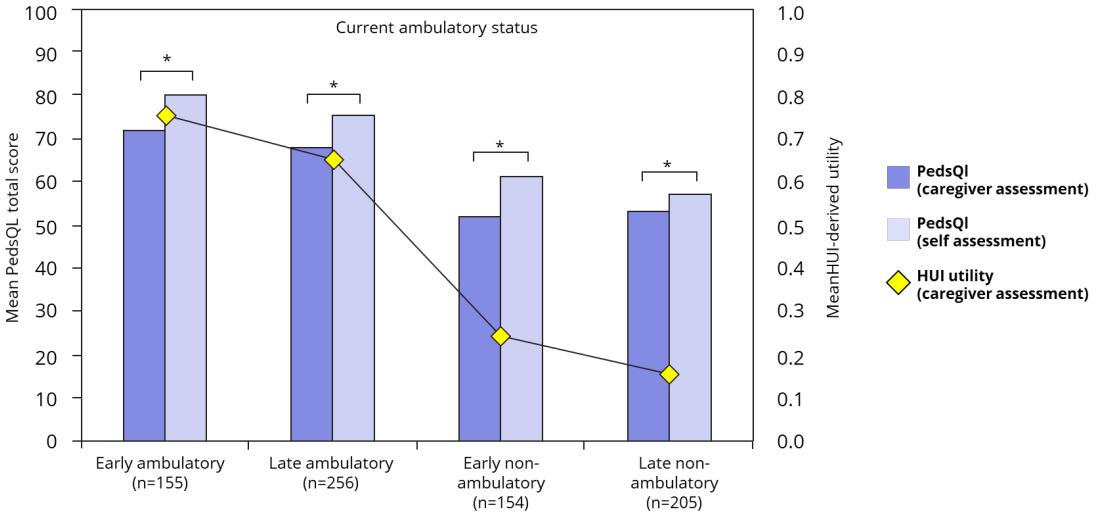
**Health-related quality of life**

Boys and young men with DMD experience significantly compromised HRQoL, which deteriorates with functional decline (Figure 7), and highlights the importance of delaying disease progression.[49] Contributing factors to this decline in HRQoL include motor and respiratory dysfunctions, muscle weakness, pain, dependence on help with daily activities, and disruptions in sleep quality.

Research funded by Duchenne UK (2023) into most common emotional and behavioural problems experienced by boys and young men with DMD reported that the most prominent difficulties they are experiencing include high levels of anxiety and worry, the feeling of being angry at themselves and annoyed with others, and sleeping problems due to excessive negative thinking or sensory overstimulation leading to extreme tiredness.[2] Parents and children agreed that further psychoeducational support is needed within the family setting but also in school and clinic environments.[2]


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**Figure 7: Self-assessed and caregiver proxy-assessed patient HRQoL by ambulatory status**




Abbreviations: HUI, Health Utilities Index; PedsQL, Pediatric Quality of Life Inventory.
Source: Landfelt, 2016.[49]

Comparisons of QoL between boys and young men with DMD and the general population reveal substantial disparities, with boys and young men with DMD consistently reporting lower HRQoL scores across a range of HRQoL measures.[48, 86]

Loss of ambulation is a key milestone in DMD disease progression, typically occurring at 12 years of age and significantly impacts patients' HRQoL.[34] When patients lose the ability to walk, their HRQoL declines (Table 5).

Preserving upper limb function in boys and young men with DMD is also important as it relates to independence and HRQoL. Worsening upper limb function correlates with a decline in HRQoL, as measured by European Quality of Life 5 dimensions 5 level version (EQ-5D-5L) scores, in individuals with DMD aged 12–40 years (Table 5).[95] In each group of participants shown, none required ventilation or had symptoms of cardiomyopathy.

**Table 5: Mean EQ-5D-5L scores in participants with DMD with declining limb function**

| Ambulation stage | Upper limb function | n | EQ-5D-5L, mean (SD) |
|---|---|---|---|
| Late ambulatory | Preserved | 6 | 0.59 (0.33) |
| Early non-ambulatory | Preserved | 2 | 0.46 (0.10) |
| Early non-ambulatory | Mildly impaired | 16 | 0.30 (0.14) |
| Late non-ambulatory | Moderately impaired | 9 | 0.22 (0.15) |
| Late non-ambulatory | Lost | 1 | 0.26 (NA) |

Abbreviations: DMD, Duchenne muscular dystrophy; EQ-5D-5L, European Quality of Life 5 dimensions 5 level version.
Source: Audhya (2023).[95]


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**Caregiver burden**

Caring for boys and young men with DMD is mentally and physically exhausting, time-consuming and complex, typically requiring multiple caregivers, e.g. both parents, siblings, grandparents or members of the wider family, alongside the multidisciplinary healthcare team. Care not only includes emotional and social support and assistance with basic and instrumental ADLs, but it also requires attendance at regular healthcare appointments and any additional visits mandated by clinical trial protocols and the associated travel, time to complete bureaucratic processes to obtain funding or various aspects of the child's care, and investment in home modifications to accommodate mobility aids and medical equipment.[2, 45, 96] While the majority of parents show high levels of resilience, studies have demonstrated that, on average, parents of those with DMD report elevated anxiety and depression.[51] Parental stress has been identified as an impediment to smooth marital and family functioning.[97] The burden for caregivers increases with disease progression, significantly impacting caregivers' overall QoL, physical, emotional and mental well-being, and employment status.[45, 56, 69, 98]

**"I liken a diagnosis of DMD as death by a thousand cuts. Because for the carers, there is never any "closure". You are given the diagnosis and you never fully come back to your pre-diagnosis mental health state. Instead, you are in state of constant readjustment, stress and anxiety as you watch your son's continual decline. And because the built world is not designed for disabled children and adults EVERYTHING is a struggle."**

*Parent of a son with DMD.*[90]

***Physical status***

Providing care to boys and young men with DMD often entails a range of physically demanding tasks that become increasingly challenging as the disease progresses.[99] A cross-sectional assessment of caregiver QoL and burden showed that caregivers of boys and young men with DMD are more likely to experience a higher prevalence of pain and discomfort compared with the reference data for the general population (44% vs. 33%, $p<0.001$) and problems performing usual activities (18% vs. 16%, $p=0.006$).[45, 69]

Over 50% of the parents of boys and young men with DMD face health issues due to the burden of their child's disease, leading to further consumption of medical treatment.[100] In a cross-sectional study assessing all boys and young men with a confirmed diagnosis of DMD or Becker muscular dystrophy (n=733) and their caregivers via the German dystrophinopathy patient registry, it was observed that parents' health status not only significantly affected their ability to provide care to their child but also impacted their work capacity, resulting in indirect costs.[100]


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### *Emotional and mental status*

Children usually present with DMD at approximately three years old, become non-ambulatory in their early teens and typically die before 30 years of age.[33, 78, 101] Therefore, unlike caregivers of children without DMD, caregivers of boys and young men with DMD face additional constraints and hidden costs that impact their health and financial well-being, extending long beyond the usual period of childhood dependency. As a result, caregivers of boys and young men with DMD have reported worse mental health, difficulty paying bills, and more hours missed from work than parents without a child diagnosed with DMD.[53]

Caregivers of boys and young men with DMD are at a notable risk of experiencing anxiety, depression, and impaired mental health, as shown in a cross-sectional study where approximately 50% of caregivers reported being moderately or extremely anxious or depressed, significantly higher than the general population ($p<0.001$).[45, 69] Such anxiety and depression stems from the social limitations, and great time devoted to caring for a boys and young men with DMD.[70] The practical consequences of caregiving resulted in 69% of caregivers neglecting their hobbies,[102] which may have otherwise provided opportunities for social connection and participation, protective factors against care-related loneliness, stress, anxiety or depression.[103] Caregivers' anxiety and depression levels often peak at diagnosis and with each milestone in the patient's disease progression, such as loss of ambulation, requirement for enteral feeding, and need for non-invasive ventilation.[51, 52] In a study of families with X-linked diseases, including DMD, guilt and stigma negatively impacted emotional well-being, particularly in carrier mothers. Carrier mothers were more likely to feel guilty ($p\leq0.01$) and blame themselves ($p\leq0.001$). In these families, fathers blamed their child's mother ($p\leq0.05$) and this sense of blame from the father was felt by the mother ($p\leq0.01$).[104] This may in part contribute to the prevalence of divorce and partnership breakdown amongst parents of boys and young men with DMD highlighted in discussions with patient advisory groups during preparation of this submission.

Profound highs and lows often mark the emotional journey of caregivers as they navigate the challenges and uncertainties associated with DMD.[45, 69] A systematic review of studies measuring the lived experience of parents of a child with DMD reported that parents experienced shock at diagnosis. At the same time, grief was an inseparable aspect of parenting an individual with DMD and guilt was also expressed due to the genetic nature of the condition.[51] Although at its most intense at the time of death of their child, similar to their experience of anxiety and depression, parents' experience of grief arose before bereavement and reached heightened states at each disease progression point.[51] The guilt experienced by carriers tends to relate to self-blame associated with the death of their son and may increase the risk of experiencing complex or prolonged grief after bereavement.[105]

Despite the impact of living with and loving someone with a rare disease of which there is very little awareness, people personally affected with DMD are rarely offered professional support to help with this impact. Only a quarter (27%) of people surveyed by Duchenne UK have been offered support, and even then it is inconsistent.[2] In recent research (2023) funded by Duchenne UK , parents confirmed that the current support received is limited and a 'postcode lottery' that mainly focuses on physical abilities, whilst neglecting the emotional and behavioural difficulties. The approach by clinicians and different services is perceived as disjointed, confusing, and frustrating.[2]


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**"When my son was diagnosed with Duchenne Muscular Dystrophy my mental health hit rock bottom. It has never recovered to pre-diagnosis levels. For the first ten years I was in a profound state of grief. Grieving for the death of a life I thought my son was going to have. And grieving for his short, disabled life. I have now come through that tunnel of grief: and what am I facing? My son is now 17, non-ambulant. I am in constant fear of his heart failing, of his breathing getting worse. And I still grieve every single day for the loss of ambulation, the loss of his arm strength, seeing the devastating impact on his loss of independence, and low feelings of self-esteem"**

*Parent of a son with DMD.*[90]

### *Carer HRQoL*

Data on carer HRQoL are available from a recent vignette study conducted by Pfizer using a time-trade-off (TTO) methodology; the study estimated the mean utility scores for eight DMD caregiver vignettes based on the health states as defined in the Project HERCULES Natural history model (NHM) (this model is described in further detail in Section B.3.3.1).[98] The study collected data via TTO interviews with 200 members of the UK general public to produce utility scores for caregivers of people with DMD (see Section B.3.4.3 for further information). The utility scores reflected the progression of the disease with higher mean utility scores in ambulatory stages (HS1 and 2) compared with later non-ambulatory stages of the disease (Table 6). The visual analogue score (VAS) scores followed a similar pattern (Table 6). These mean utility values demonstrate a continuous, nearly linear decline in caregivers' HRQoL, attributed to the escalating demands of their caregiving responsibilities. The increasing demands and complexities associated with DMD described above (such as boys/young men losing their ability to perform activities of daily living, requiring ventilation support, and assistance with mobility) consistently increase the burdens and expectations placed upon caregivers. These data reveal that the HRQoL significantly diminishes not only for boys/young men with DMD, but also for their caregivers, thereby impacting the broader family and social unit.[98]

**Table 6: Mean utility scores and mean VAS scores through eight DMD HS carried out with members of general public**

| | HS1 | HS2 | HS3 | HS4 | HS5 | HS6 | HS7 | HS8 |
|---|---|---|---|---|---|---|---|---|
| **Utility score** | 0.72 | 0.67 | 0.58 | 0.56 | 0.50 | 0.54 | 0.51 | 0.48 |
| **VAS score** | 65.49 | 57.01 | 42.33 | 42.44 | 38.13 | 37.79 | 33.36 | 31.67 |

Note: Scores obtained from TTO task evaluating vignettes detailing the progression of DMD across multiple domains; each of the 200 participants scored each health state; people with DMD can enter HS5 or HS6 only and will then progress directly from either to HS7.
Abbreviations: DMD, Duchenne muscular dystrophy; HS, health state; TTO, time-trade-off; VAS, visual analogue scale.
Source: DoF (Pfizer Caregiver vignette study in DMD, 2024).[98]


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Duchenne UK argue strongly that carer HRQoL must be included in HTAs of new treatments for DMD.[2] They believe that while carer HRQoL is currently sometimes considered in a qualitative way, this means there is uncaptured value in a product which cannot be translated into anything that is useful for a quantitative-focused quality-adjusted life year (QALY). Including a caregiver HRQoL metric would change dramatically the cost effectiveness arithmetic of medicines for rare diseases and complex paediatric progressive life-limiting conditions.[2]

**Burden on siblings and the wider family**

The childhood of siblings without DMD is also significantly affected. About one-third of parents believe that DMD has a negative influence on the psychological well-being and social life of the unaffected siblings.[102] Siblings often run the risk of being “voiceless” and may feel invisible to parents focused on the complex needs of their child with DMD.[106, 107] Siblings describe themselves as having to manage their emotional pain on their own, as they are unable to share it with a family system that is under significant pressure.[106] At the time of bereavement, the loss of a sibling is a highly traumatic event and may be more disruptive than the loss of other family members.[108]

While parental burden is high in DMD, the growing burden of disease progression on the family means that even siblings may be required to contribute to caregiving duties.[99] Many siblings give up time with friends, sports or extracurricular activities and/or travel.[53, 99] This can lead to practical and psychological difficulties for the sibling, including a negative impact on their social life (such as school performance and involvement in leisure activities) and their emotional well-being (such as fear, aggression, or withdrawal).[28]

**Burden on school settings**

The developmental period from the teenage years through the twenties is a time of profound transition to increased independence and adult role attainment. However, the most significant changes in a child’s physical ability will occur during their school years, and the presence of additional learning needs and behavioural difficulties is common in children with DMD.[1, 54]

Although DMD has principally been studied in the context of skeletal muscle dysfunction, it is a multisystem disorder because dystrophin is also expressed in cardiac and smooth muscle, endocrine glands, and neurons.[109] Consistent with dystrophin's functional importance in the central nervous system, boys and young men with DMD often exhibit varying degrees of non-progressing cognitive impairment, with their intelligence quotients (IQ) shifted downward one standard deviation below the normal range.[110–112] Moreover, boys and young men with DMD have difficulty communicating and a higher prevalence of social behaviour problems, poor facial affect recognition, obsessive-compulsive disorder and autism spectrum disorder than the general population.[47, 113–115] Rates of speech delay (74 of 192 participants; 39%), learning difficulties (49 of 178 participants; 28%) and inattentive-overactive behaviour (14 of 183 participants; 8%) were reported in a study of 196 steroid-naïve boys aged between 4 and 8 years.[116]

Therefore, specialist support and adaptations or modifications to the classroom environment will be required to ensure children with DMD can reach their potential.[1, 54] In a study of school experiences of boys with DMD, non-ambulatory students had a significantly greater


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prevalence of needing a teaching assistant and additional support compared to those who were ambulating, suggesting that schools and local authorities need to plan to allocate greater resources for boys with DMD as they grow older and more physically disabled.[117] However, a survey by Duchenne UK (2023) found that boys with DMD and their families were struggling with a lack of awareness of DMD at school, with only 10% thinking that those who worked in education had a good understanding of the disease.[2] This leaves pupils with DMD vulnerable when at school, and many experience bullying by other pupils.

**"Our son's mental health is affected when his teachers don't understand or have any empathy even though they have had his neuromuscular care advisor go in to school to talk about DMD."**

*Parent of a child with DMD.*[2]

### Economic burden

Data, especially in non-ambulant children in real-world settings, is difficult to capture; however, overall, the economic burden of DMD is high. The total annual costs of DMD encompass a spectrum of components, including hospital admissions, visits to physicians and practitioners, tests and assessments, medications, nonmedical community services, aids, devices, investments, informal care, and indirect costs. In the UK, of the total cost of illness for DMD, 26% relate to indirect costs, 20% to medications, and 27% to nonmedical community services.[56]

*Direct costs*

The average cost associated with the care and treatment of boys and young men with DMD was estimated to be ten times higher than that of the cost incurred by the overall population in a cross-sectional study of boys and young men with DMD and their caregivers from Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, and the UK.[55] The annual mean per-patient direct costs for DMD were estimated at €42,360, €23,920, and €54,160, respectively (Table 7) in an international study that estimated the total cost of illness and economic burden associated with DMD in Germany, Italy, and the UK.[56]

**Table 7: Estimation of total cost of illness and economic burden associated with DMD in three European Countries**

| Country | Annual Mean Per-Patient Direct Costs of DMD (€) | Annual Mean Household Burden of DMD (€) | Total Annual Economic Burden of DMD (€) |
|---|---|---|---|
| Germany | 42,360 | 70,190 | 27M |
| Italy | 23,920 | 58,440 | 1M |
| UK | 54,160 | 63,600 | 200M |

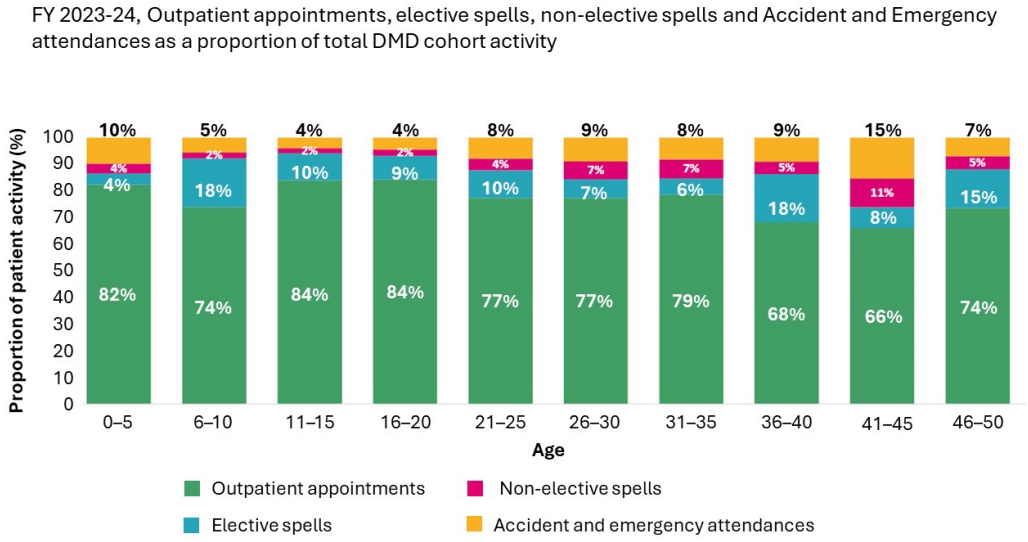
Abbreviations: DMD, Duchenne muscular dystrophy; M, Million; UK, United Kingdom.
Source: Landfeldt, 2014.[56]


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Rehabilitation services (e.g. physiotherapy, occupational therapy, and speech and language therapy) and the costs of medical aids were shown to represent the main drivers for direct medical costs, accounting for 50% of the direct annual costs of DMD.[56] Costs increased after the loss of ambulation when patients became full-time wheelchair users and required respiratory support.[56, 57] The main drivers for nonmedical direct costs relate to community nursing support in the home and the costs associated with car and home adaptations required to accommodate the consequences of disease progression.[100]

In an analysis of Hospital Episode Statistics (HES) data undertaken by the company, the majority of healthcare activity was delivered through outpatient appointments across all age groups (Figure 8). Boys and young men with DMD managed their conditions predominantly through outpatient appointments throughout their life. Elective spells were notably a greater proportion of activity in the 6-10 years age group, which may be associated with the loss of ambulation. Non-elective and emergency care activity showed some increase in the older age groups, which may relate to difficulties with disease progression.

**Figure 8: Proportion of acute and outpatient activity by age group, HES analysis**




Abbreviations: DMD, Duchenne muscular dystrophy; FY, financial year; HES, Hospital Episode Statistics.
Source: Data on file ITF Pharma UK.[36]

Inpatient activity for children was concentrated in specific specialities, while adults showed more variability in their inpatient spells (Figure 4). Childhood non-elective activity was concentrated in paediatrics, cardiology, trauma, and orthopaedics, whereas adulthood non-elective activity was largely in general internal medicine and respiratory medicine. During childhood, elective activity was concentrated in paediatric neurology, endocrinology, and respiratory medicine services. In adults, elective activity was spread across neurology, respiratory medicine, and other specialities.[36]

*Indirect costs*

DMD imposes substantial financial stress upon affected families, impacting productivity, employment status, and other aspects of life. Moreover, this impact on families and caregivers increases as the disease progresses.[52] The indirect costs of DMD are associated with household caregiving responsibilities and increase significantly as the disease


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progresses. In an international, cross-sectional study, the mean annual household burden for DMD was estimated at between €58,440 and €71,900. The costs vary across different countries, with Germany incurring €70,190, Italy €58,440, and the UK €63,600 in indirect costs. The total economic burden of DMD, including the monetary value of the loss in patient and caregiver QoL in Germany, Italy, and the UK, was estimated at €278,058,000, €154,465,000, and €200,478,000, respectively (Table 7).[56]

DMD contributed to a loss of working capacity, resulting in lost working time and overall loss of productivity in a German cross-sectional study assessing all boys and young men with a confirmed diagnosis of DMD or Becker's muscular dystrophy (n=733) and their caregivers. Half of boys and young men with DMD were non-workers; of those who worked, the majority stopped working or reduced working hours when they reached the early non-ambulatory stage.[100]

The same study reported that 89% of patients received part- or full-time care from another person who was the parent in 93% of the cases. Caregivers often resigned from their employment (30%), reduced working hours (38%) on average by 15 hours per week, and missed a mean of 14.5 working days per year due to their child's disease. In addition, 60% of caregivers expressed that their career pursuits were constrained, and 49% reported reduced earnings due to their son's condition.[100]

***Mortality costs***

For diseases with no or minimal excess mortality, the costs incurred for living patients provide an adequate estimate of their economic burden to society. However, for diseases with a high mortality rate, such as DMD, the total aggregated national cost remains relatively low due to the disease's low prevalence, even though it places a substantial burden on individual patients. Consequently, diseases with high mortality may appear less costly to society despite the significant value of the life years lost. Therefore, mortality costs are a crucial factor when analysing the overall burden.[118]

A 2012 study assessing the mean annual mortality cost of DMD in Germany, Italy, the UK, and the US estimated the life years lost due to DMD based on the incidence of the condition for each country and subsequently calculated the mortality cost using a willingness-to-pay of €75,000 per life-year gained. The study showed that the national mortality cost of DMD was €335M for Germany, €248M for Italy, €267M for the UK, and €1,208M for the US.[118]

### B.1.3.7 Current treatment pathway and proposed givinostat positioning

**Goals of treatment**

DMD is a complex, multisystem disease managed by a multidisciplinary team. There is no cure for DMD. The goal of treatment is to allow boys and young men with DMD to experience as much of childhood as possible by slowing the progressive trajectory of muscle loss thereby maintaining independence and delaying the time to loss of ambulation and loss of upper limb function.


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### UK HTA recommendations

A summary of completed and discontinued UK HTA is shown in Table 8. To date, there is only one positive reimbursement recommendation for treatments for DMD in England/Wales and Scotland; this is for ataluren in a small subgroup of patients with a specific gene mutation and was conducted under NICE's Highly Specialised Technology process.[7]

**Table 8: HTA recommendations for DMD**

| HTA body | Type | Recommendation |
|---|---|---|
| NICE | Guideline | NG127: Suspected neurological conditions: recognition and referral[119] |
| | Highly specialised technologies guidance | HST22: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene[7] |
| | Highly specialised technologies guidance (d*iscontinued)* | Eteplirsen for treating Duchenne muscular dystrophy[120] |
| | Highly specialised technologies guidance (d*iscontinued)* | Drisapersen for the first-line treatment of Duchenne muscular dystrophy[121] |
| | Single technology appraisal (*discontinued)* | Idebenone for treating Duchenne muscular dystrophy[122] |
| SMC | *Ultra-orphan pathway* | Ataluren (Translarna) for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged two years and older[123] |

Abbreviations: DMD, Duchenne Muscular Dystrophy; SMC, Scottish Medicines Consortium.

### Current treatment guidelines

There are no UK-specific clinical practice guidelines for managing DMD, and clinicians working in the UK generally follow recommendations in guidance published by the International DMD Care Considerations working group, which was last updated in 2018.[11, 43, 124] DMD Care UK has established 11 working groups, each focused on one of a wide range of clinical care areas for boys and young men with DMD, including adult, psychosocial, physiotherapy, nutritional, orthopaedic, and surgical care.[80] As a consequence of this workstream, to date DMD Care UK has created UK-focused bone/endocrine, cardiac, and respiratory standards of care based on the recommendations in the international guidance.[125]

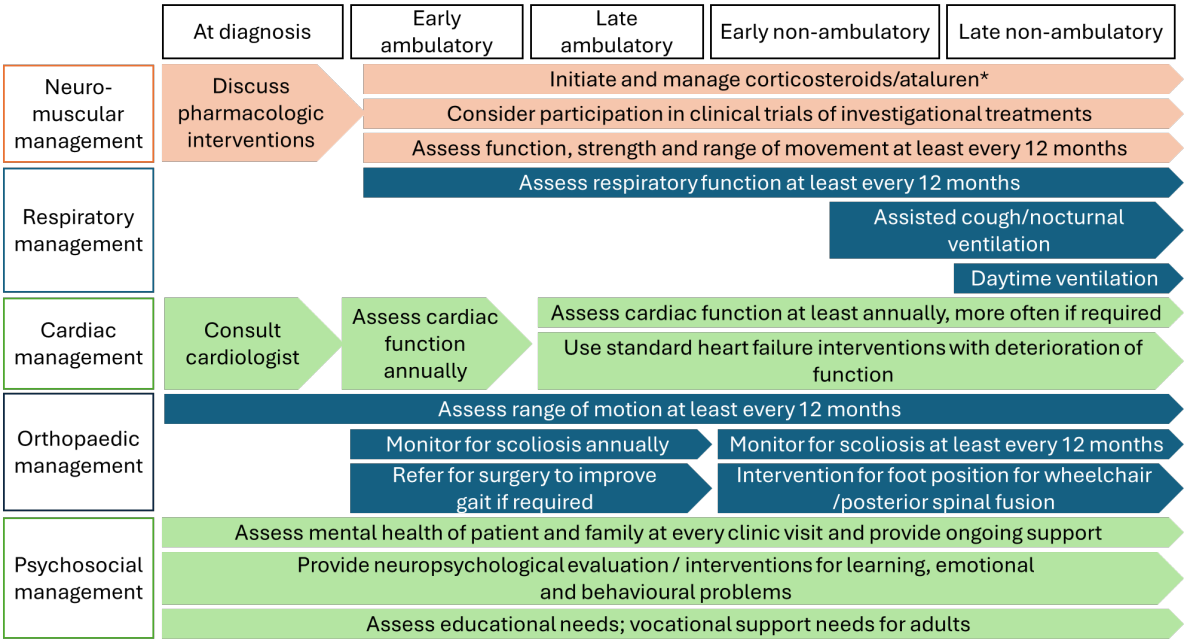
### Current UK treatment options for DMD

A multidisciplinary approach focused on medical, surgical, and rehabilitative interventions, including physiotherapy and orthotics, that target the symptoms of DMD is essential to positively impact the disease's natural course, potentially improving both QoL and longevity.[11, 13, 43, 124, 125] The limited treatment options available to boys and young men with DMD mean that consideration for enrolment in clinical trials is an important part of the treatment pathway.


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The UK treatment pathway for DMD in patients aged six years and over is shown in Figure 9.

**Figure 9: UK treatment pathway for DMD in boys ≥6 years of age**




*Ataluren is indicated and reimbursed only in children aged two years and over with a nonsense mutation in the dystrophin gene.
Abbreviations: DMD, Duchenne muscular dystrophy.
Sources: Adapted from Birnkrant et al. 2018,[11, 43] DMD Care UK;[125] Bourke J et al. 2022.[126]

*Established clinical management (ECM)*

ECM for boys with DMD in England and Wales includes physiotherapy, CS and other supportive care. CS, particularly deflazacort and prednisone, act as anti-inflammatory and immunosuppressive agents, supporting control of symptoms, maintaining muscle strength, and delaying loss of ambulation.

Despite not being indicated in the UK for the treatment of DMD, CS are started once the diagnosis of DMD is established and continue from the early ambulatory Phase (5 to 7 years old) through the late physical manifestations of the disease, continuing until clinicians consider their side effects outweigh the benefit of their use. UK corticosteroid prescribing patterns between 2012–2022 were identified from the NorthStar database, which prospectively collects longitudinal data from all children with DMD followed in all 24 UK paediatric neuromuscular centres. Data on corticosteroid usage was available for 1,096 patients across 6,521 observations; 800 patients (73%) were taking CS. The most commonly prescribed corticosteroid was prednisolone; 544 patients were taking prednisolone on at least one observation. The most common regime was daily (526 patients) rather than intermittent dosing. Deflazacort was observed in 183 (41%) assessments, with daily dosing reported in 292 (67%) assessments.[127]


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However, the efficacy of long-term corticosteroid use remains uncertain due to poor adherence and clinically relevant AEs, including excessive weight gain, hypertension, glucose intolerance, increased bone fracture risk, and mood modulation, leading to patient dissatisfaction.[13, 28, 75, 128] In the analysis of NorthStar data, there were significantly higher rates of reporting mild appetite changes in the prednisolone group (32%) vs. the deflazacort group (27%), p=0.036. The deflazacort group had a higher rate of reporting other side effects compared with the prednisolone group: mild gastrointestinal (GI) symptoms 14% vs. 8%, p<0.001; moderate/severe cushingoid appearance 32% vs. 19%, p<0.001; mild insomnia 15% vs. 11%, p<0.001. The daily regime had higher rates of side effects when compared to the intermittent regime for appetite issues, GI symptoms and cushingoid appearance (p=0.016, p<0.001 and p<0.001, respectively). [127] The UK HERCULES Project identified fractures (vertebral and long bone), obesity, and delayed puberty as AEs of greatest concern to parents, whereas short stature, obesity, and cushingoid features were of greatest concern to patients.[129]

A modified corticosteroid, vamorolone, has a marketing authorisation in Great Britain but is not reimbursed by the NHS and is not part of the routine clinical management of DMD.[130]

*Ataluren*

Ataluren was granted a conditional marketing authorisation in the European Union in July 2014 for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged two years and older, accounting for only 10% to 15% of boys and young men with DMD. The primary endpoint for the pivotal Phase 3 trial was not met, resulting in conditional approval from the EMA.[5]

In June 2024, the EMA confirmed the recommendation of non-renewal of the marketing authorisation for ataluren, as a full re-evaluation of the medicine's benefits and risks and the results of a new study failed to confirm ataluren's effectiveness.[6] It is unclear whether the MHRA will also review the marketing approval for ataluren in the UK based on this data, and as such, its future use in routine clinical practice is uncertain.

**Unmet need**

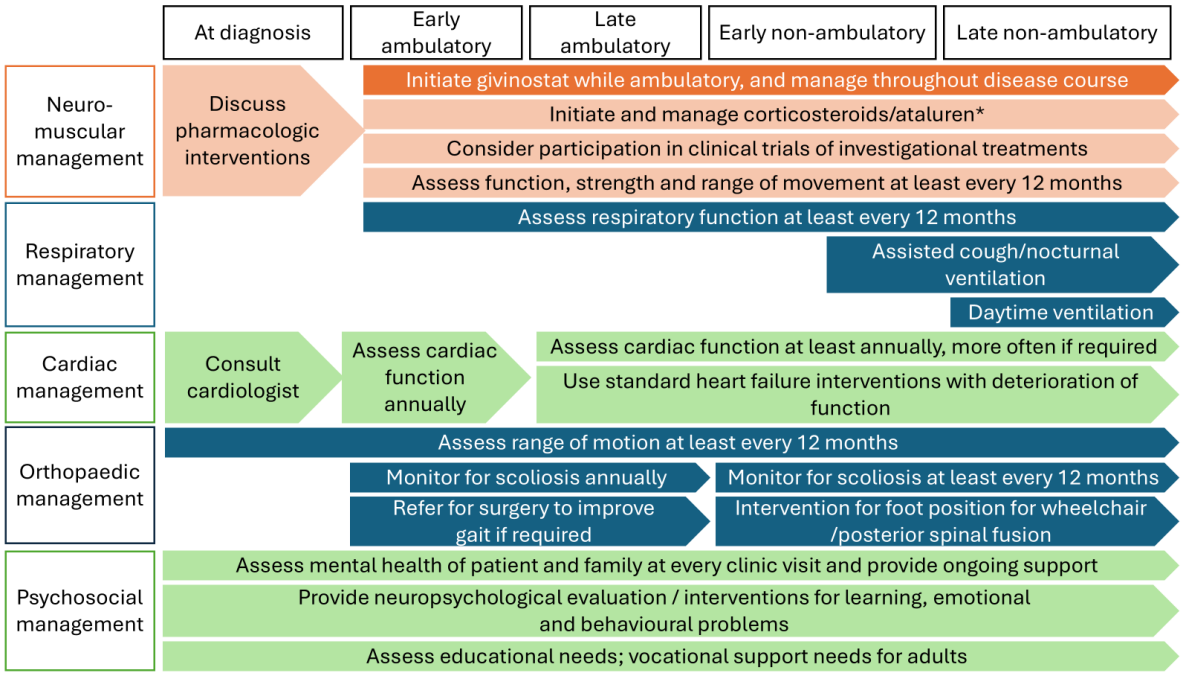
Introducing CS into ECM was shown to delay loss of ambulation, preserve upper limb and respiratory function, and reduce the need for scoliosis surgery.[131] Since then, no innovative therapies have demonstrated clinically meaningful and statistically significant improvements in functional primary endpoints for boys and young men with DMD compared with ECM. There is a high unmet need for a new therapy that is available to boys with DMD that demonstrates a clinically meaningful and statistically significant improvement in functional endpoints compared with the current standard of care regardless of specific dystrophin gene mutation type.

**Proposed place of givinostat in the current treatment pathway**

The proposed place in therapy for givinostat is as an add-on therapy to ECM (including CS), as shown in Figure 10. Givinostat is not intended to displace corticosteroid use in clinical practice.


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**Figure 10: Proposed place in therapy for givinostat**




*Ataluren is indicated and reimbursed only in children aged two years and over with a nonsense mutation in the dystrophin gene.
Abbreviations: DMD, Duchenne muscular dystrophy.
Sources: Adapted from Birnkrant et al. 2018,[11, 43] DMD Care UK.[125]

## *B.1.4 Equality considerations*

DMD affects both children and young adults. Age is protected under the Equality Act. Therefore, any difference in access to treatment based on age may raise potential equality issues.

DMD affects mostly boys; presentations in girls can occur but are rare. Sex is a protected characteristic under the Equalities Act. Therefore, any differences in access to treatment based on sex may raise potential equality issues. Further studies are needed to establish the possible effect of givinostat on girls and young women with DMD.

Many boys and young men with DMD have mobility difficulties or use adaptive equipment or assistive devices such as manual or power wheelchairs, and they have accessibility needs. Given the level of disability boys and young men with DMD experience, restrictions on the centres able to prescribe or administer givinostat may raise concerns about travel accessibility and duration.

A significant proportion of people with DMD have poor outcomes because of learning or behavioural difficulties, ADHD, autism, and pre-existing psychiatric difficulties.[2] A significant proportion of people with DMD cannot have corticosteroids because of these issues and have worse outcomes.

DMD is a rare condition and there is limited access to comprehensive studies and inclusion in novel therapeutic randomised controlled trials.


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# B.2 Clinical effectiveness

**Givinostat efficacy has been demonstrated in an extensive, ongoing clinical trial programme which includes the pivotal Phase 3 Epigenetic Rescue of Dystrophin Dysfunction Study (EPIDYS; Study 48),[22, 132] the ongoing Open-label extension (OLE; Study 51),[133] and the Phase 1/2 Study 43[18]**

- EPIDYS was a multicentre, 18-month, randomised, double-blind, placebo-controlled trial in ambulatory boys with DMD aged ≥6.[22, 132] It is one of the largest randomised DMD trials to date:
  - Target intention-to-treat (ITT) (Group A) population (boys with baseline magnetic resonance spectroscopy [MRS)] vastus lateralis muscle fat fraction; [VL MFF] >5% to 30%) was used for the prespecified efficacy analyses (N=120)[22, 132]
  - Overall ITT (Safety) population was used for safety evaluations and *post hoc* supportive efficacy analyses (N=179)[22, 132]
- Data from the ongoing OLE study[134, 135] provide additional supportive evidence of givinostat's efficacy and safety in boys with DMD – and provide one of the longest follow-up periods of any clinical study programme for a new therapy for DMD

**DMD is a progressive disease, causing decline in muscle function over time. Givinostat significantly slowed the rate of disease progression at 18 months compared with ECM**[22, 132]

- Non-log-transformed data showed a reduction of approximately 40% in the decline in 4-stair climb (4SC) over 18 months for givinostat vs. placebo (a 1.78 seconds smaller decline with givinostat);[22, 132] this difference was apparent from Week 48.[22, 132]
- This statistically significant reduction in the decline in time to perform 4SC is clinically relevant and correlates with increased participation in physical and social activities of daily life and predicts delayed loss of ambulation[22, 132]

**Givinostat also slowed the decline in functional outcomes relating to daily activities, slowed decline in muscle strength, and slowed fat fraction infiltration in the leg muscles at 18 months compared with ECM**[22, 132]

- Givinostat showed numerically less decline in North Star Ambulatory Assessment (NSAA) total score than with placebo, at 18 months (least squares [LS] mean difference 1.9; 95% confidence interval [CI] 0.3 to 3.5; nominal p=0.021).[22, 132, 136] Boys receiving givinostat were more likely to be still able to run, jump, hop and rise from a chair at 18 months than those who received placebo[22, 132]
- Cumulative loss of function was numerically lower with givinostat than with placebo (2.14 fewer items failed over 18 months; nominal p=0.0202);[22, 132, 136] This is important because a loss of 2.0 NSAA items predicts clinically meaningful disease progression and loss of ambulation in a functionally declining group[137]
- Muscle strength, evaluated by knee extension or elbow flexion (and normalised by subject weight; N/kg), showed numerically less decline with givinostat than with placebo at 18 months[22, 132]
- Treatment with givinostat reduced fat infiltration in VL muscle versus placebo by approximately 30% (LS mean difference for givinostat-placebo: –2.9%; nominal p=0.035).[22, 132, 136] This is considered to be clinically meaningful, because increased VL MFF inversely correlates with muscle function, daily activity (4SC and time to rise from the floor [TTRF]) and predicts loss of ambulation

**Overall, reductions in the rate of decline in ambulatory ability seen in EPIDYS are strongly suggestive of a delay in the loss of ambulation for boys with DMD, and are expected to delay disease progression more generally as patients' DMD progresses**

**Givinostat treatment showed a trend towards a reduction in the decline of the HRQoL for boys with DMD at 18 months, compared with the placebo group,[136] likely reflecting slower disease progression**


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**A *post hoc* supportive analysis of the efficacy of givinostat in the overall ITT population confirmed that the results were consistent with those seen in the prespecified analyses reported above for the Target ITT (Group A) population**[138]

**For boys continuing (n=177) – or starting (n=30) – givinostat treatment in the ongoing (non-placebo controlled) OLE study, results were consistent with EPIDYS**[134, 135, 139]

- Descriptive analysis of the efficacy results indicate a slight deterioration in muscle function for ambulant boys, but also that givinostat delays the occurrence of major disease milestones[135, 139]
- Median age at loss of ambulation was 16.7 years,[135] which is higher than expected in boys and young men with DMD treated with CS alone (11 years 8 months in a 2022 analysis of UK North Star data)[73]
- For the 12 boys and young men who were non-ambulant when entering the OLE study, upper limb muscle strength remained almost the same after up to 6 years of treatment. As expected with a progressive disease, there was some deterioration in Egen Klassifikation (EK) score and Barthel Index Total Score over the follow-up period of up to 6 years[135]

**Results from an indirect treatment comparison (ITC) conducted by the company indicate that patients treated with givinostat will be significantly older at loss of ambulation compared with patients treated with ECM without givinostat, as well being significantly older when requiring non-invasive ventilation and when reaching FVC <1L (acceleration factor used to provide estimated age for non-ambulatory outcomes)**

**EPIDYS demonstrated a predictable and manageable safety profile for givinostat. AEs were more frequent in the first 3 months of treatment and were generally manageable through dose reduction or interruption**[22, 132, 140]

- Treatment compliance was high in EPIDYS, and 95% of boys overall completed the study[22, 132]
- Treatment-related AEs were more common with givinostat than with placebo; these were typically known to be associated with givinostat treatment (e.g. diarrhoea, thrombocytopaenia, and hypertriglyceridaemia).[22, 132] However, these were generally manageable with dose modification. None of the severe or serious AEs were treatment-related or resulted in study withdrawal, and no boys died during the study[22, 132]

**Dec 2023 data cut off (DCO) safety results from the ongoing OLE study confirm that givinostat has a predictable and acceptable safety and tolerability profile consistent with EPIDYS and other studies of givinostat**[139]

- Treatment compliance remained high[139]
- There were no new safety signals in the OLE study at Dec 2023 DCO[135]

**Overall, the results show that givinostat significantly slows the trajectory of the DMD muscle impairment, reduces decline in muscle mass and potentially delays loss of ambulation and other major disease milestones, compared with ECM**

The appraisal population comprises boys and young men with DMD who are ambulant when they initiate givinostat. This is a subpopulation of the anticipated GB marketing authorisation.[1] Data describing the efficacy of givinostat in ambulant boys are from the Phase 3 EPIDYS study and from the ongoing OLE study (Study 51). The latter study currently includes boys from both the Phase 1/2 Study 43[141] and the Phase 3 EPIDYS study,[22, 132] in which all boys/young men are receiving a weight-based dose of givinostat oral suspension 10 mg/mL bid (until commercial availability/reimbursement of givinostat in the respective study country).[133, 136]


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## B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify randomised controlled trials (RCTs) for givinostat and ECM for the management of DMD. Full details of the methodology and results of the SLR are provided in Appendix D.

## B.2.2 List of relevant clinical effectiveness evidence

The SLR (Appendix D) identified one journal article[22] (and several posters/abstracts) relating to a Phase 3, placebo-controlled study (EPIDYS; see Table 9 for details) that provides evidence on the efficacy and safety of givinostat for the treatment of ambulant boys aged ≥6 years with DMD. Only very limited data from the ongoing OLE study have been published[142] and most of the evidence from this study that is used in the cost-effectiveness model (CEM) is unpublished (see Table 10 for study details). The CEM utilises the OLE study data via an indirect treatment comparison (see Section B.2.8 for further details).

Published data relating to a Phase 1/2 study (Study 43), an open-label study to evaluate givinostat safety, tolerability, pharmacokinetics (PK), and effects on histology and clinical parameters, were also identified but are not used in the CEM (see Section B.2.10.1). A Phase 3 study, ULYSSES (Study 50) is ongoing in non-ambulant boys aged ≥9 to <18 years, who have not previously received givinostat.[143]

**Table 9: Clinical effectiveness evidence (EPIDYS)**

| | |
|---|---|
| **Study** | EPIDYS (Study 48; NCT02851797) |
| **Study design** | Phase 3, randomised, double-blind, placebo-controlled, multicentre |
| **Study geography** | UK, US, Canada, Belgium, France, Germany, Israel, Italy, Netherlands, Serbia, Spain |
| **Population** | Ambulant boys aged ≥6 years at baseline affected by DMD |
| **Intervention(s)** | Boys in the study were randomised 2:1 to receive givinostat or placebo, both in addition to ECM, twice-daily (morning and evening) after a meal, as an oral suspension administered using a graduated dosing syringe<br>A flexible treatment regimen was used, with a fixed starting givinostat dose, selected according to body weight (to maximise efficacy), but with dose reductions prespecified if AEs occurred (to retain an acceptable and manageable safety and tolerability profile)<br>• The weight-based starting dose initially ranged from 20–70 mg bid, with a reduced dose of 13–47 mg bid (Regimen 1)<br>• Following a protocol amendment (based on 18 June DCO analysis of blinded safety haematologic data) the starting dose was changed to 13–47 mg bid, with a reduced dose of 11–37 mg bid, for boys who were recruited after the amendment (Regimen 2)<br>See Appendix M.2 for full details of the two dosing protocols |
| **Comparator(s)** | Placebo (in addition to ECM), twice-daily (morning and evening) after a meal, as an oral suspension administered using a graduated dosing syringe |


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| | |
|---|---|
| **Indicate if study supports application for marketing authorisation** | Yes |
| **Indicate if study used in the economic model** | Yes |
| **Rationale for use/non-use in the economic model** | Pivotal study in ambulant boys; provided data for the Marketing Authorisation Application and represents the primary evidence base in the submission |
| **Reported outcomes specified in the decision problem** | • Walking ability (ambulation): 6MWT, **age at loss of ambulation during the study**, 10MWT<br>• Muscle function: 4SC, TTRF, NSAA<br>• Muscle strength: knee extension; elbow flexion as measured by HHM<br>• Ability to undertake activities of daily living (NSAA)<br>• Lung function<br>• Cardiac function<br>• Number of falls<br>• Lower body function<br>• Health-related quality of life (assessed by PODCI)<br>• Mortality<br>• **Adverse effects of treatment** |
| **All other reported outcomes** | • Mean change in VL MFF<br>• PK-PD analyses |
| **Key publication** | Mercuri et al. 2024[22] and Supplementary appendix[132] |
| **Secondary sources** | • EPIDYS CSR (10 August 2022)[136]<br>• Mercuri et al. 2023[144]<br>• Mercuri et al. 2024b[138]<br>• Vandenborne et al. 2023[145]<br>• Vucinic et al. 2024[140] |

Outcomes listed in bold are included in the economic model.
Abbreviations: 10MWT, 10-metre walking test; 4SC, 4-stair climb; 6MWT, 6-minute walking test; bid, twice daily; DCO, data cut off; DMD, Duchenne muscular dystrophy; ECM, established clinical management; EPIDYS, Epigenetic Rescue of Dystrophin Dysfunction; HHM, hand-held myometry; MFF, muscle fat fraction; NSAA, North Star Ambulatory Assessment; PK-PD, pharmacokinetic/pharmacodynamic; PODCI, Paediatric Outcomes Data Collection Instrument; TTRF, time to rise from the floor; VL, vastus lateralis.


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**Table 10: Clinical effectiveness evidence (OLE study)**

| | |
|---|---|
| **Study** | OLE (Study 51; NCT03373968) |
| **Study design** | Open-label, multicentre, long-term study |
| **Study geography** | UK, US, Canada, Belgium, France, Germany, Israel, Italy, Netherlands, Serbia, Spain |
| **Population** | Boys/young men with DMD aged ≥6 years old who had participated in Study 43 or EPIDYS, or met all the inclusion for the EPIDYS overall population but were not randomised. This study will also eventually include boys/young men who have completed ULYSSES (Study 50) and Study 52 |
| **Intervention(s)** | Givinostat oral suspension (10 mg/ml) bid after a meal, in combination with ECM, including standard CS therapy<br>Flexible treatment regimen (see Table 14) |
| **Comparator(s)** | None; open-label study |
| **Indicate if study supports application for marketing authorisation** | Yes |
| **Indicate if study used in the economic model** | Yes |
| **Rationale for use/non-use in the economic model** | Provides long-term data in ambulant and non-ambulant givinostat-treated boys |
| **Reported outcomes specified in the decision problem** | • **Adverse events of treatment**<br>• Walking ability (ambulation) 6MWT, **time to LOA** and **age at LOA**<br>• Muscle function: 4SC, 10MWT, TTRF, 6MWT, NSAA, PUL V1 and V2, MFM<br>• Muscle strength: knee extension, elbow flexion<br>• Ability to undertake activities of daily living<br>• Respiratory function: **time to non-invasive ventilation**, **age at non-invasive ventilation**, age at respiratory support needed during the day, **time to FVC<1L, age at FVC<1L, time to FVC<30%, age at FVC<30%**<br>• Health-related quality of life (people with DMD): PedsQL, SF-36<br>• Age at major disease milestones |
| **All other reported outcomes** | • Change in physical function from baseline in the EK score<br>• Barthel Index Total Score<br>• Age at scoliosis surgery<br>• Age at death |
| **Key publication** | Not published |
| **Secondary sources** | DoF (Study 51 Clinical Study Report; Dec 2023 DCO)[135] |

Outcomes listed in bold are included in the economic model.
Abbreviations: 10MWT, 10-metre walking test; 4SC, 4-stair climb; 6MWT, 6-minute walking test; bid, twice daily; DCO, data cut off; DMD, Duchenne muscular dystrophy; ECM, established clinical management; EK; Egen Klassifikation; HHM, hand-held myometry; LOA, loss of ambulation; MFM, motor function measure; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; PedsQL, Pediatric Quality of Life Inventory; PFT, pulmonary function tests; PUL V1 and V2, Performance of Upper Limb version 1 and 2; SF-36, 36-Item Short Form Health Survey; TTRF, time to rise from the floor.


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### *B.2.3 Summary of methodology of the relevant clinical effectiveness evidence*

The overall ongoing clinical development programme for givinostat in DMD covers boys aged ≥2, and both ambulant and non-ambulant populations (Figure 11).

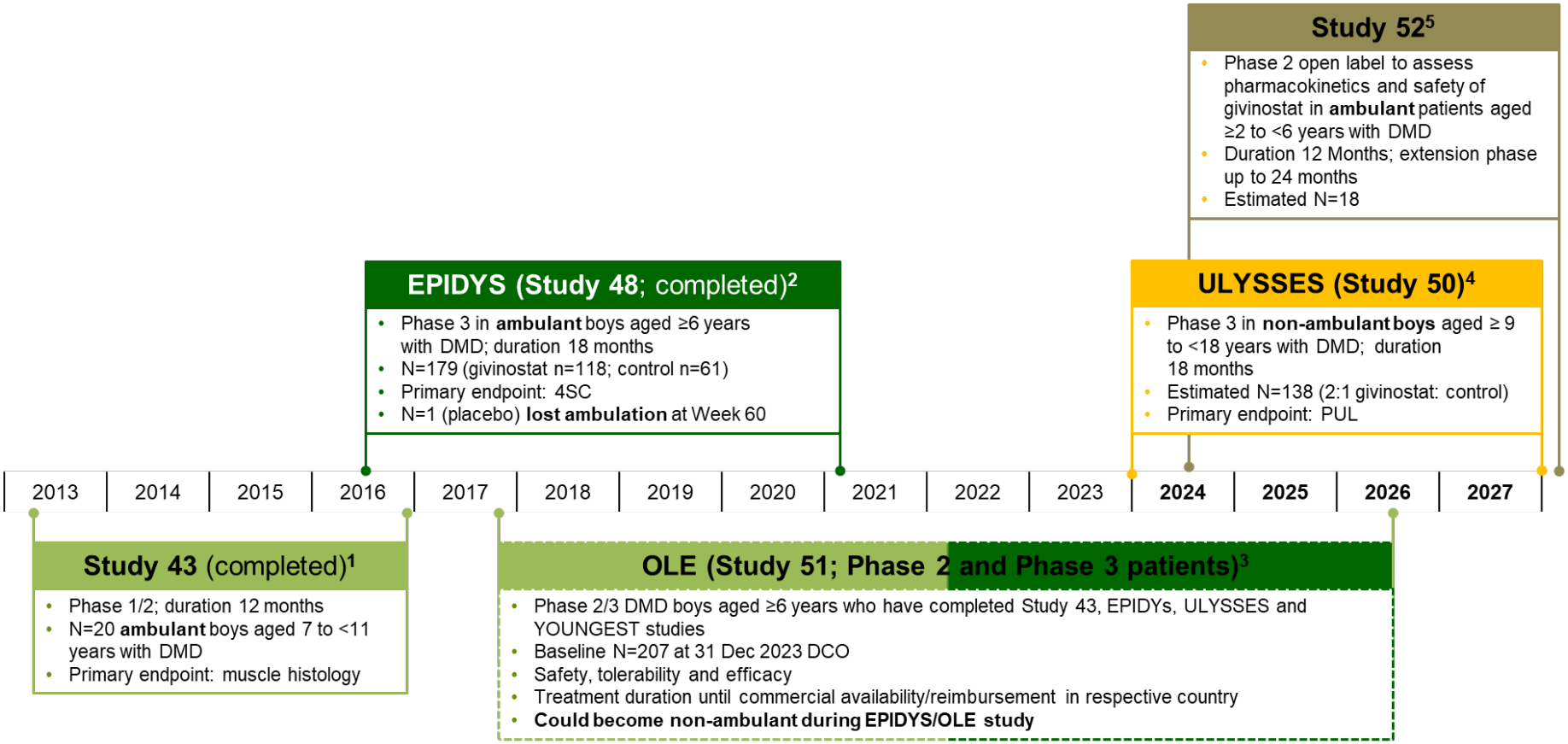
The pivotal Phase 3 RCT, EPIDYS (Study 48) study included ambulant boys aged ≥6 years with genetically confirmed DMD who had received stable systemic CS for at least 6 months.[22, 132] Prespecified efficacy analyses use the Target ITT (Group A) EPIDYS population (N=120); these boys were selected based on their thigh muscle fat fraction (VL MFF) to ensure a selection of boys who would likely retain ambulation during the 18 month study period and to provide the greatest opportunity of powering the study to show a significant treatment difference versus placebo (in what is a small disease population overall; see Section B.2.3.1 and Section B.2.4.3).[22, 132] The wider, overall EPIDYS ITT population was recruited so that the safety of givinostat could be evaluated in a broader population of boys with DMD (N=179).[22, 132] As described in Section B.2.6.4, the efficacy results from the overall ITT population are consistent with the Target ITT population,[22, 132] and therefore the efficacy results from this Overall ITT population are used to inform the CEM to use the largest population for which efficacy data are available.

The Phase 1/2 Study 43[141] and the Phase 3 EPIDYS study[22, 23, 136] included ambulant boys. Boys from both of these studies were able to subsequently enrol in an ongoing OLE study (Study 51) of givinostat efficacy and safety, which may include men aged >18 years as the study population ages.[133] The OLE study is therefore providing longer-term outcomes for givinostat, as well as some information for boys who are non-ambulant.[133] These data (December 2023 data cut) are included in the CEM because they provide longer follow-up.[135]

An additional Phase 2 Study 52 to assess the pharmacokinetics and safety of givinostat in younger boys is ongoing as part of the Paediatric investigation plan.[146] This study includes ambulant boys aged ≥2 to <6 years with DMD; core study results are anticipated in May 2027 and extension phase results are due in September 2029. The ongoing Phase 3 placebo-controlled ULYSSES (Study 50) is recruiting non-ambulant boys aged ≥9 to <18 years of age; results are anticipated in mid-2028.[143]


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**Figure 11: Givinostat clinical development programme in DMD**




Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walk test; DCO, data cut off; DMD, Duchenne muscular dystrophy; MRS, magnetic resonance spectroscopy; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; PK, pharmacokinetics; PUL, Performance of the Upper Limb.
Sources: 1. ClinicalTrials.gov. NCT01761292;[141] 2. ClinicalTrials.gov. NCT02851797;[23] 3. ClinicalTrials.gov. NCT03373968;[133] 4. ClinicalTrials.gov. NCT05933057;[143] 5. EMA, 2023.[146]


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### B.2.3.1 EPIDYS | Study design

EPIDYS is a completed multicentre, randomised, double-blind, placebo-controlled, Phase 3 study.[22, 132] The study duration was planned for 19 months and was comprised of two phases:[22, 132, 136]

- Screening period: starting 4 weeks (±2 weeks) before randomisation. During the screening period, time to 4SC test was to be performed at Visit 1 and 2
- Double-blinded treatment period: 18 months of treatment (72 weeks).

Eligible study participants were ambulant boys aged ≥6 years with genetically confirmed DMD, who completed two 4SC assessments with a mean of ≤8 seconds (≤1 seconds variance), had a time-to-rise of ≥3 seconds but <10 seconds, and had received stable systemic CS for at least 6 months (with a reasonable expectation that CS dose and regimen would not change over the duration of the study).[22, 132]

Recruitment was prespecified in two groups:[22, 132]

- Target ITT population (Group A) consisting of boys with baseline VL MFF of >5% but ≤30%
- Group B consisting of those with a VL MFF of ≤5% or >30%.

The Target ITT (Group A) was intended to comprise boys who were not at risk of sudden, complete loss of ambulation but who, if receiving placebo, would show sufficient decline over the study duration in the function, strength, and fat fraction endpoints being tested. These criteria were based on expert opinion, were subsequently published, and are consistent with the recommendations of a consensus workshop on DMD outcome measures.[22, 132] Group B was recruited so that the safety of givinostat could be evaluated in a broader population of boys with DMD.[22, 132]

The main exclusion criteria were any surgery or medication change in the previous 3 months that could affect muscle strength or function, or a loss of ankle plantar flexion of ≥30° (detailed inclusion and exclusion criteria are included in Appendix M.1).[22, 132]

Boys were randomised with a 2:1 ratio to receive:[22, 132]

- Group 1 (n=118): givinostat oral suspension (10 mg/ml), 2 times daily (after a meal), in combination with ECM, including standard CS therapy
- Group 2 (n=61): placebo oral suspension (10 mg/ml), 2 times daily (after a meal), in combination with ECM, including standard CS therapy.

The 2:1 randomisation ratio was chosen, as due of the rapidly progressive nature of DMD and the rarity of the disease, this ratio maximised the number of boys exposed to active treatment while maintaining study integrity.[22, 132] Randomisation was stratified by concomitant CS use in four strata according to CS type (deflazacort or other CS) and regimen (daily or intermittent), to help to ensure balance between the randomised treatment arms.[22, 132] Boys, investigators, and site and sponsor staff were masked to treatment assignment, and the placebo suspension was indistinguishable in appearance and taste from givinostat.[22, 132]


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The initial doses of givinostat were based on a dose ranging evaluation in a mouse model,[17] in addition to the results of the previous Phase 2 study in boys with DMD[18] and several studies of other disorders.[22, 132] A flexible treatment regimen was used, in which a fixed starting dose of givinostat was given to maximise efficacy but dose reductions were prespecified if AEs occurred, such as platelet count reduction or diarrhoea.[22, 132] The weight-based starting dose was initially 20–70 mg oral givinostat twice a day, with a reduced dose of 13–47 mg twice a day (see Regimen 1; Appendix M.2). A protocol amendment following the masked safety review (in June 2018), reduced the starting dose to Regimen 2 (Appendix M.2) for boys who were recruited after the amendment. The starting dose for Regimen 2 was 13–47 mg twice a day, with a reduced dose of 11–37 mg twice a day. A subsequent protocol amendment, applying only to France, moved all boys to Regimen 2.[22, 132]

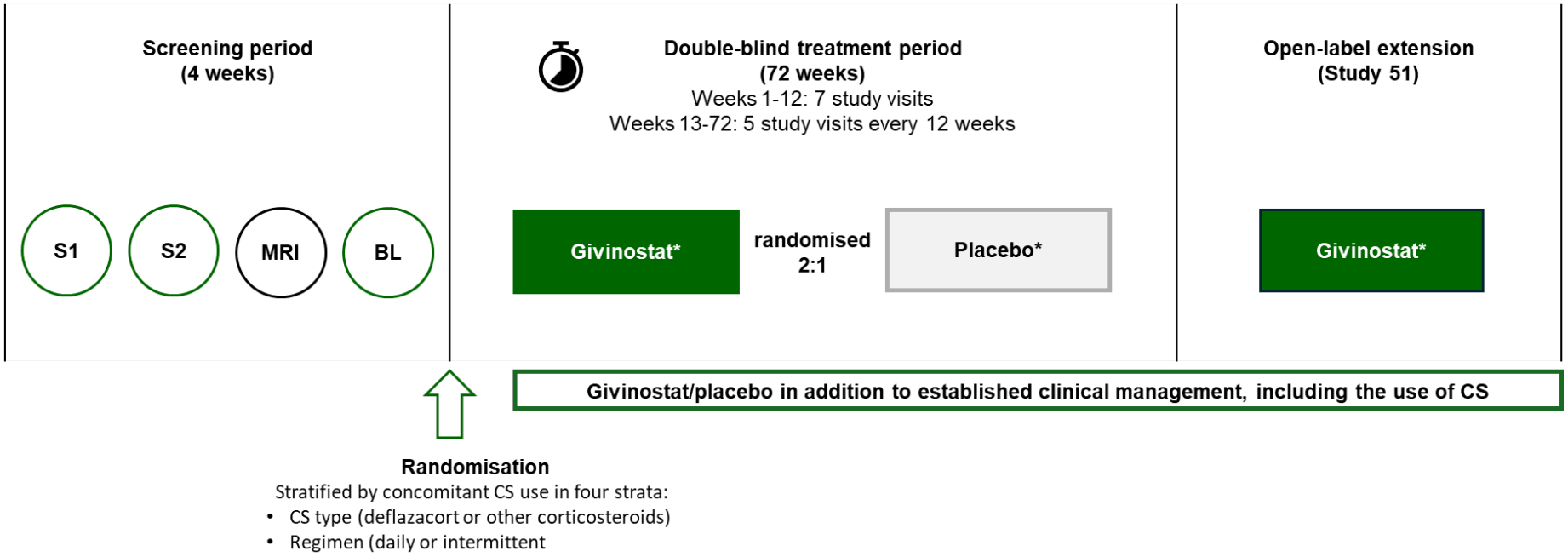
If boys gained weight during the study, the drug dose was kept unchanged; if boys lost weight the dose was adjusted as per Supplementary Table 46 in Appendix M.2.

Note that in the EPIDYS study, the strength of givinostat is expressed as “givinostat hydrochloride monohydrate”[136] whereas it is expressed as “givinostat free base” in the draft UK SmPC. 10 mg/ml givinostat hydrochloride monohydrate is equivalent to 8.86 mg/ml givinostat free base.[147]

A summary of the study designs is shown in Figure 12 and the study methodology in Table 11.


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**Figure 12: EPIDYS | Study design**




Notes: Two MRI/MRS assessments occurred during the 72-week double-blind treatment period; *in addition to established clinical management, including the use of CS: in the givinostat arm 20% and 80% of boys were treated with prednisone/other and deflazacort, respectively and in the placebo group arm, 23% and 77% of boys were treated with prednisone/other and deflazacort, respectively.
Abbreviations: BL, baseline; CS, corticosteroids; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; n, number of patients in the study population; S, screening.
Sources: Mercuri et al. 2024[22, 132]; ClinicalTrials.gov. NCT02851797.[23]


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**Table 11: Summary of EPIDYS methodology**

| | |
|---|---|
| **Study design** | Phase 3, multicentre, randomised, double-blind, placebo-controlled |
| **Duration of study** | 4-week screening, 18 months (72 weeks) treatment |
| **Settings and locations where data were collected** | 41 tertiary care sites in 11 countries (Belgium, Canada, France, Germany Israel, Italy, the Netherlands, Serbia, Spain, the UK, and the USA) |
| **Participant eligibility criteria** | **Key inclusion criteria (see Appendix M.1.1 for full inclusion criteria)**<br>• Ambulant boys aged ≥6 years with genetically confirmed DMD<br>• Completed two 4SC assessments with a mean of ≤8 seconds (≤1 second variance)<br>• Time-to-rise from floor of ≥3 seconds but <10 seconds<br>• Manual muscle testing of quadriceps Grade ≥3<br>• Received stable systemic CS for ≥6 months (with a reasonable expectation that CS dose and regimen would not change over the duration of the study)<br>• Willing to use adequate contraception |
| | **Key exclusion criteria (see Appendix M.1.2 for full exclusion criteria)**<br>• Any surgery, treatment or medication change in the previous 3 months that could affect muscle strength or function<br>• Loss of ankle plantar flexion of ≥30°<br>• Presence of other clinically significant disease<br>• Platelet, white blood cell, and haemoglobin counts at screening <lower limit of normal; fasting triglycerides >300 mg/dL<br>• Symptomatic cardiomyopathy or heart failure or LVEF <50% at screening; liver disease or impairment, inadequate renal function<br>• Positive test result for hepatitis B surface antigen, hepatitis C antibody, or HIV at screening.<br>• Baseline corrected QT interval >450 msec, or history of additional risk factors for torsades de pointes<br>• Psychiatric illness/social situations preventing understanding/compliance with the muscle function tests and/or with study protocol procedures<br>• Any hypersensitivity to the components of the study drug; sorbitol intolerance or sorbitol malabsorption, or the hereditary form of fructose intolerance<br>• Contraindications to MRI or spectroscopy |
| **Study drugs** | Randomised in ratio 2:1, stratified by stratified by concomitant CS type (deflazacort or other CSs) and regimen (daily or intermittent)<br>**Intervention (administered orally):**<br>• Givinostat oral suspension (10 mg/ml) bid after a meal, in combination with ECM, including standard CS therapy<br>• Starting dose and permitted dose reduction was selected according to body weight (see Appendix M.2)<br>– Regimen 1: 20–70 mg oral givinostat bid, with a reduced dose of 13–47 mg bid<br>– Regimen 2: 13–47 mg oral givinostat bid, with a reduced dose of 11–37 mg bid<br>• If boys gained weight during the study, the drug dose was kept unchanged; if boys lost weight the dose was adjusted as per the table in Appendix M.2 |


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| | |
|---|---|
| | **Comparator (administered orally):**<br>• Placebo oral suspension (10 mg/ml), bid after a meal, in combination with ECM, including standard CS therapy |
| **Concomitant medication** | **Permitted concomitant medication**: stable CS treatment; medications to treat minor treatment-emergent illnesses (generally permitted); supportive treatments, such as antiemetics, anti-diarrhoeals, antipyretics, antiallergics, analgesics, and antibiotics; Vitamin D, calcium, and any other supplements if clinically indicated before enrolment and for the duration of the study<br>**Prohibited concomitant medication**: any other investigational drug; any dystrophin restoration product; and use of any pharmacologic treatment, other than CS, that might have an effect on muscle strength or function (e.g. growth hormone) |
| **Primary outcomes** | Mean change in 4SC before and after 18 months of treatment with givinostat versus placebo |
| **Other outcomes used in the economic model/specified in scope** | • Walking ability (**age at loss of ambulation**)<br>• Time to rise from floor<br>• Muscle function<br>• Muscle strength<br>• Ability to undertake activities of daily living<br>• Bone function<br>• Cardiac function<br>• Concordance and optimisation of treatment<br>• Endocrine function<br>• **Lung function**<br>• Time in wheelchair<br>• Number of falls<br>• Time to scoliosis<br>• Lower body function<br>• Upper body function<br>• Mortality<br>• **Treatment-related adverse effects of treatment**<br>• Health-related quality of life (people with DMD and carers) |
| **Other outcomes of interest** | • Compliance<br>• Dose modification |
| **Pre-planned subgroups (4SC)*** | • Maintained treatment for >80% of the time versus those who did not (equivalent to total % compliance)<br>• Total weight adjusted exposure (mg/kg) < versus ≥ median total weight adjusted exposure (mg/kg)<br>• Started on the higher givinostat dose (Regimen 1) versus those who started on the lower dose (Regimen 2)<br>• DMD mutation (deletion, duplication, point mutation)<br>• LTBP4 genotype (IAMM, VTTT, other)<br>• SPP1 genotype (TT, GT, GG)<br>• Age at first dose (6–7 years versus >7 years) |

Outcomes listed in bold are included in the economic model.
*Additional subgroup analyses were performed for the key secondary endpoints; see Section 11.1.3.2 of the EPIDYS CSR[136] for results.
Abbreviations: 4SC, 4-stair climb; CS, corticosteroids; DMD, Duchenne muscular dystrophy; HIV, human immunodeficiency virus; LTBP4, latent transforming growth factor β-binding protein 4; MRI, magnetic resonance imaging; SPPI, secreted phosphoprotein 1 (osteopontin); LVEF, left ventricular ejection fraction.
Source: Mercuri et al. 2024;[22, 132] ClinicalTrials.gov. NCT02851797;[23] EPIDYS CSR[136]; EPIDYS SAP.[148]


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### B.2.3.2 EPIDYS | Study outcomes

Study endpoints and their definitions are shown in Table 12. The primary endpoint, all key secondary efficacy variables and exploratory endpoints were formally assessed at baseline and after 18 months of treatment.[22, 132] All safety endpoints were formally assessed at baseline and end of study. Boys, investigators, and site and sponsor staff were masked to treatment assignment, and the study personnel who did the efficacy analyses differed from those who recorded and reviewed the safety results, to mitigate the risk of unmasking.[22, 132]

**Table 12: EPIDYS | Summary of key endpoints**

| Endpoint/assessment | Definition/measurement |
|---|---|
| **Primary endpoint** | |
| Change in the results of the standard 4SC assessment between baseline and 18 months | Mean change in time to climb 4 standard stairs before and after 18 months of treatment of givinostat vs. placebo. Baseline 4SC was the measurement taken at the randomisation assessment unless this was missing, in which case baseline was taken as the last non-missing value recorded prior to or on the date of first study treatment. In addition to the 4SC recorded in seconds, functional adaptation employed by the boy during the test was evaluated and graded by functional evaluators according to standardised scales: 1) unable to climb up 4SC; 2) climbs 4SC 'marking time' (climbs one foot at a time, with both feet on a step before moving to next step), using both arms on one or both handrails; 3) climbs 4SC 'marking time' (climbs one foot at a time, with both feet on a step before moving to next step), using one arm on one handrail; 4) climbs 4SC 'marking time' (climbs one foot at a time, with both feet on a step before moving to next step), not needing handrail; 5) climbs 4SC alternating feet, needs handrail for support; 6) climbs 4SC alternating feet, not needing handrail support |
| **Key secondary endpoint** | |
| Change from baseline after 18 months in NSAA total score | Change from baseline in the total NSAA score to after 18 months of treatment with givinostat or placebo. The 17 items of the NSAA, ranging from ability to stand to ability to run 10 metres, were graded using a standard score card with each assessment rated as 0: unable to achieve independently; 1: modified method but achieves goal independent of physical assistance from another, or 2: normal with no obvious modification of activity. The total NSAA score was calculated as the sum of the scores for each of the items. Where ≥1 scores for the 17 items were missing at a visit, the relevant rules described in Table 15 were followed |
| NSAA cumulative loss of function | The boy's cumulative number of failures across all post-baseline visits was the endpoint of interest for analysis (sum of the total failures at each post-baseline visit). For each boy at each post-baseline visit, failure to perform each of the 17 items of the NSAA was assessed, where 'failure' was defined as a score transition from 2 or 1 at baseline to 0 at the respective visit. The total number of failed items for the visit was calculated (maximum of 17 failed items per |


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| Endpoint/assessment | Definition/measurement |
|---|---|
| | visit per boy). In addition, total failed items at baseline were calculated for each boy as the number of items with a score of 0 at the baseline NSAA assessment. |
| Time-to-rise from floor (TTRF) | Mean change from baseline in time to rise from the floor after 18 months of treatment with givinostat vs. placebo. Time to rise from the floor was also be graded by functional evaluators according to standardised scales: 1) unable to stand from supine, even with use of a chair; 2) assisted Gowers': requires furniture for assist in arising from supine to full upright position; 3) full Gowers': rolls over, stands up with both hands 'climbing up' the legs to achieve full upright posture; 4) half Gowers': rolls over, stands up with one hand support on leg; 5) rolls to the side and/or stands up with one hand or both hands on the floor to start to rise up but does not touch legs; 6) stands up without rolling over or using hands. Where boys stopped the test prematurely, this was equivalent to not completing the test and therefore the missing time to rise from floor were imputed (Table 15) |
| Distance walked in 6 minutes (6MWT) | Mean change from baseline in 6MWT after 18 months of treatment with givinostat vs. placebo. Boys who stopped the test prematurely were still included in the summaries, plots and analyses of the total distance walked by the end of the test and the number of falls |
| Muscle strength evaluated by knee extension | Mean change from baseline to 18 months after treatment with givinostat vs. placebo in muscle strength was evaluated by knee extension and elbow flexion. These muscle strength variables were measured by HHM. If more than one measurement was taken, the arithmetic mean of the measurements was used for that visit for that particular boy |
| Muscle strength evaluated by elbow flexion measured by HHM | |
| Mean change in VL MFF | Mean change in VL MFF was assessed by MRS before and after 18 months of treatment with givinostat vs. placebo. Analysis of this endpoint only applied to the MR cohort, i.e. those who completed MR assessment at baseline, 12 and 18 months |
| **Quality of life endpoint (patient reported outcomes) \| Exploratory endpoint** | |
| PODCI | The PODCI quality of life questionnaire was completed by the boy's parent or the boy himself. A total of 5 subscales (upper extremity function; transfer and basic mobility; sports and physical functioning; pain/comfort and happiness) and 1 global function scale were calculated from the questionnaire. The endpoints of interest were the change from baseline to 18 months in the standardised scores for each subscale and the global function scale, as completed by the parent and the boy |
| **Safety endpoints** | |
| AEs and SAEs | AEs were coded using the MedDRA Dictionary Version 24.1. AE defined as an AE that started or worsened on or after the date of start of the administration of the IMP. If the relationship to study drug was unknown, the AE was assumed to be related to the study drug. If a boy experienced >1 AE, the boy |


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| Endpoint/assessment | Definition/measurement |
|---|---|
| | was counted once at the worst severity and at the most related event |
| Vital signs and clinical laboratory test results (blood chemistry and haematology) | **Haematology**<br>All results were converted to SI units for the purposes of summaries, plots and listings. Statistics of haematology observed values and change from baseline by parameter and visit were presented by treatment group for all boys in the Safety population.<br>**Blood chemistry**<br>Clinical chemistry results were summarised for the following parameters: triglycerides, total cholesterol, total bilirubin, cystatin C and creatinine. Data for the following liver function parameters were listed separately: AST, ALT, GGT, urinalysis, coagulation, and serology |
| Respiratory function | Pulmonary function change from baseline was evaluated using $FEV_1$ (L), FVC (L), $FEV_1$/FVC (%) and PEF (L/min) |
| Cardiac function evaluated by ECG and echocardiogram | Cardiac function was assessed as change from baseline in a 12-lead resting ECG and standard echocardiogram in the Safety population |
| Cognitive function | Evaluated by the Raven-coloured progressive matrices performed at screening and at Visit 18. |
| Weight, height, and BMI | Collected at baseline |
| Evaluation of acceptability/palatability of the oral suspension | Acceptability and palatability of IMP was assessed at Week 4 and end of study (Week 72) or Boy withdrawal (boys who withdraw early). Boy's perceptions of the medicine, parent's perception of the medicine based on the boy's reaction and whether there were problems administering the medication were summarised by visit and treatment group |

Abbreviations:4SC, 4-stair climb; 6MWT, 6-minute walking test; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ECG, electrocardiogram; EU, European Union; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; GGT, gamma glutamyl transpeptidase; HHM, hand-held myometry; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; MFF, muscle fat fraction; MR, magnetic resonance; MRS, magnetic resonance spectroscopy; NSAA, North Star Ambulatory Assessment; PEF, peak expiratory flow; PODCI, Paediatric Outcomes Data Collection Instrument; SAE, serious adverse event; SI, Système International; TTRF, time to rise from the floor; VL, vastus lateralis.
Source: Mercuri et al. 2024;[22, 132] EPIDYS CSR (2022);[136] EPIDYS SAP (2022).[148]

### B.2.3.3 EPIDYS | Choice of and clinical relevance of the efficacy endpoints

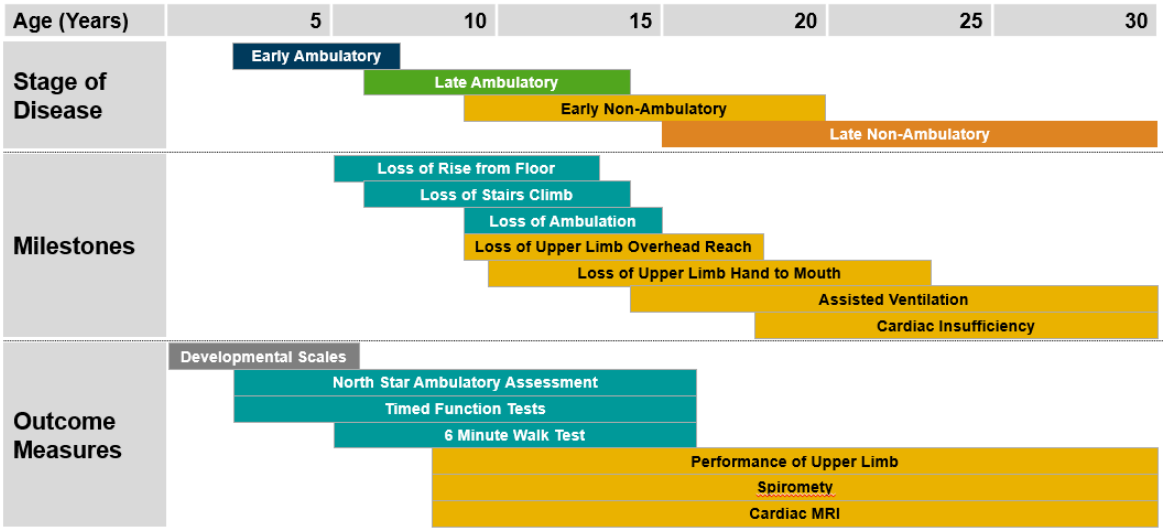
No specific outcome measure is recommended as a primary endpoint in DMD clinical studies, as no single test evaluates disease evolution in all muscle groups. Regulatory bodies recommend that applicants evaluate treatment effects using multiple tests in support of the selected primary outcome measure.[149, 150]


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### Functional tests

Milestones indicative of disease progression, such as loss of ability to rise from the floor, climb stairs and walk unassisted, can be predicted by timed functional tests that are reliable measures of functional ability. These milestones also correlate with specific stages of the disease (Figure 13).[151, 152]

**Figure 13: Correlation of stages of DMD with milestones and outcomes measures**




Abbreviations: DMD, Duchenne muscular dystrophy; MRI, Magnetic Resonance Imaging.
Source: Adapted from Lynn, 2015.[152]

Measures of strength, timed motor performance, and pulmonary function have been well described and validated by clinicians and clinical researchers in DMD. Timed motor performance evaluations such as the TTRF, 4SC and the time to walk/run 10 metres (10MWT) are commonly used as clinical trial outcome measures, are reliable measures of functional ability, are endorsed by DMD clinical guidelines and regulatory agencies and have been used widely in DMD clinical trials.[151, 152]


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**Table 13: Outcome measures indicative of key disease ambulation milestones in DMD progression**

| Outcome measures | Description | Key findings |
|---|---|---|
| Four-stair climb (4SC)[50, 151, 153–156] | Critical measure of lower limb strength and power, evaluating the time taken for the patient to climb up and down four standard-sized stairs | Predict the loss of the ability to climb stairs over 2 years, the loss of ambulation, and the time to 10% decline in ambulatory capacity<br>A slower 4SC correlated with reduced participation in physical and social activities of daily living and predict loss of stairs-climbing ability and ambulatory capacity<br>Duration of 4SC affects the HRQoL measure PODCI with higher baseline 4SC, leading to greater declines.<br>4SC is highly correlated with knee extension strength |
| North Star Ambulatory Assessment (NSAA)[156–160] | The NSAA is a key instrument for measuring clinical outcomes in boys and young men with DMD, encompassing tasks like standing, walking, running, climbing stairs, rising from the floor, and lifting objects<br>It is a comprehensive, clinician-rated, and patient-centred 17-item rating scale designed to evaluate the motor abilities of ambulant boys and young men with DMD<br>Each item can be scored as 0 (unable to perform), 1 (modified method but performed goal independently) or 2 (able to perform independently with no obvious modifications) | Total scores on the NSAA range from 0 to 34, with higher scores indicating better ambulatory function and functional performances<br>NSAA total score correlates with the 6MWD and other outcome assessments used in boys and young men with DMD<br>The NSAA score was 13 at 11 years old and decreased to 9 units at 12, with a median age of loss of ambulation of 13 years |
| Six-minute walking distance (6MWD)[152, 153, 156, 161–163] | Evaluates the endurance and functional capacity of boys and young men with DMD by measuring the distance they can walk on a flat, hard surface in 6 minutes, typically measured along a 60-metre level course<br>It is well-established, reproducible, and well-tolerated in ambulatory boys and young men with DMD<br>Challenges relating to 6MWD use include limitations in statistical power owing to cross-patient variability<br>A number of trials have used the 6MWT as a primary endpoint. However, the 6MWT has come under some criticism. TFTs offer potentially appealing alternative primary endpoints for use in ambulatory patients | Baseline distance influences the rate of progression of 6MWD.<br>Data from a study suggested that if the distance walked in 6 minutes was at least 330 metres at baseline, the risk of losing ambulation within two years was significantly reduced<br>For every 30-metre incremental decrease in the baseline 6MWD, the percentage of patients who remained ambulatory over the following two years decreased substantially |
| Ten-metre walking test (10MWT)[151, 156] | Measures the time it takes to walk/run 10 metres | Completing the task in more than 12 seconds was predictive of loss of ambulation within the next 12 months |


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| | | |
|---|---|---|
| | | with a high statistical significance (100%; p< 0.0001)<br>Boys and young men with DMD who could perform the task in less than 6 seconds were significantly more likely to maintain ambulatory ability for longer (100%; p< 0.0001) |
| Time to rise from the floor (TTRF)[156, 161, 162, 164] | Measures the time in seconds taken to stand up from lying supine on the floor to a straight standing position without help<br>Important indicator of functional mobility and is crucial for understanding a patient's ability to perform daily activities | The mean 12-month 6MWD change was -30.49 metres, -6.23 in those with a baseline TTRF within 7 seconds, and -77.84 in those with more than 7 seconds<br>TTRF declines rapidly over time in boys and young men with DMD and is a prognostic factor of 12-month changes in the 6MWD and for disease progression and loss of ambulation |

Abbreviations: 4SC, 4-stair climb; 6MWD, 6-minute walking distance; 6MWT, 6-minute walking test; 10MWT, 10-metre walking test; DMD, Duchenne muscular dystrophy; HRQoL, health-related quality of life; NSAA, North Star Ambulatory Assessment; PODCI, Pediatric Outcomes Data Collection Instrument; TFT, timed function tests; TTRF, time to rise from the floor.

**Choice of 4SC as the primary efficacy outcome in EPIDYS**

The time to climb 4 standard-sized stairs (4SC) is a clinically meaningful, reliable and validated timed motor function test that is a widely used clinical study endpoint in DMD,[154, 158, 165, 166] and is required by the EMA 2015 and Food and Drug Administration 2018 Guidelines. It is widely used as an endpoint in DMD trials and has shown to be predictive of DMD progression milestones, including loss of ambulation, loss of ability to climb stairs over two years and time to 10% decline in ambulatory capacity (Table 13).[151]

It objectively measures a clinically meaningful 'lifechanging' impact on a patient's overall health, as well as being predictive of future decline.[151, 165] In EPIDYS, the measurement was performed by qualified functional evaluators (physiotherapists) in a standardised manner.[167] Climbing stairs requires lower limb muscle strength and a range of motion from the leg joints; even small differences in 4SC are multiplied many times across a day for a child with DMD. Although 4SC has been used as an endpoint in DMD studies for decades, as it is reproducible and simple to administer, it is less widely used in clinical practice due to a lack of standardised equipment outside of research centres.

The key secondary endpoints (cumulative loss of function in the NSAA, change in TTRF, change in the 6-minute walking distance [6MWD] and change in strength) include the parameters that are considered relevant in this population to corroborate the results obtained from the primary 4SC endpoint.[136]


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### B.2.3.4 EPIDYS | Assessment timepoints and follow-up

The screening period started 4 weeks (±2 weeks) before randomisation.

The boys attended study site visits every 12 weeks for 18 months. At every visit, the boys completed a 4SC, the NSAA (including time-to-rise from the floor), a 6-minute walking test (6MWT) and muscle strength assessment (knee extension and elbow flexion, by standardised hand-held myometry).[22, 132] All functional and strength assessments were evaluated by trained physiotherapists masked to treatment and other assessments, with all baseline and 72-week visits recorded and reviewed by an expert, independent team of physiotherapists, not otherwise involved in the study, for quality assurance.[22, 132] MRS of the right upper leg was done at after 48 and 72 weeks, with the images centrally read by an independent team of MRS experts, not otherwise involved in the study, for the calculation of VL MFF.[22, 132] Drug compliance was assessed using diary data.[22, 132]

Appendix Table 47 (in Appendix M.4) outlines the timing of procedures and assessments performed throughout the study.

### B.2.3.5 Open-label extension (OLE) study | Study design

The OLE study (Study 51, NCT03373968) is an ongoing multicentre, open-label, long-term study to assess the safety, tolerability, and efficacy of givinostat.[133–135, 139] It includes boys with DMD previously enrolled in either Study 43 or EPIDYS, and also includes 30 givinostat-naïve patients with DMD (boys screened in EPIDYS who met all the inclusion criteria and none of the exclusion criteria but were not randomised because the enrolment in the Off-target group was complete).[133] All boys receive givinostat oral suspension 10 mg/mL bid (dose adjusted according to weight) until commercial availability or reimbursement of givinostat in the respective study country.

There are three treatment groups:[135]

- The **givinostat group** comprises boys randomised to givinostat in their previous givinostat study (n=119 at 31 Dec 2023 DCO)
- The **delayed givinostat group** comprises boys randomised to placebo in their previous givinostat study (n=58 at 31 Dec 2023 DCO)
- The **naïve givinostat group** comprises DMD subjects screened in EPIDYS who met all the inclusion criteria and none of the exclusion criteria and were not randomised because the enrolment was completed (n=30 at 31 Dec 2023 DCO).

At the cut-off date of the fifth interim analysis (31 Dec 2023), 207 boys had been enrolled.[135] Of these, 21 had prematurely discontinued the study.[135] The mean actual duration of givinostat treatment was 1,177 days (standard deviation [SD] 453 days; range 26 to 2,259 days).[135] The median duration of givinostat treatment was 1,162 days or approximately 3.2 years.[135]

The maximum givinostat exposure in the OLE was 6.1 years,[135] but 16 patients were previously treated for up to 4 years in Study 43, giving a maximum total exposure time of 10.1 years.[135, 168]


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**Table 14: Summary of OLE study methodology**

| | |
|---|---|
| **Study design** | Open-label, multicentre, long-term study |
| **Duration of study** | Until commercial availability/reimbursement of givinostat in the respective study country. |
| **Settings and locations where data were collected** | 39 tertiary care sites in 11 countries (Belgium, Canada, France, Germany Israel, Italy, the Netherlands, Serbia, Spain, the UK, and the USA) |
| **Participant eligibility criteria** | **Key inclusion criteria**<br>• Had participated in one of the previous studies with givinostat in DMD (Study 43 or EPIDYS) and had attended the End of Study Visit<br>• Or had been screened in EPIDYS and:<br>o Met all the inclusion criteria and none of the exclusion criteria<br>o Had a baseline VL MFF assessed by MRS in the range ≤5% or >30%, i.e. included in 'Off-target' group<br>o Were never randomised because the enrolment in the Off-target group was completed<br>• Aged ≥6 years old<br>• Were able to give informed assent and/or consent<br>• Subjects used adequate contraception |
| | **Key exclusion criteria**<br>• Use of any pharmacologic treatment, other than CS, that had an effect on muscle strength or function within 3 months prior to enrolment<br>• Use of any investigational drug other than givinostat<br>• Presence of any other clinically significant disease<br>• Platelet, white blood cell, and haemoglobin counts at screening <lower limit of normal; fasting triglycerides >300 mg/dL<br>• Heart failure, liver disease or impairment, inadequate renal function<br>• Baseline corrected QT interval >450 msec, or history of additional risk factors for Torsades de pointes<br>• Psychiatric illness/social situations preventing understanding/compliance with the muscle function tests and/or with study protocol procedures<br>• Any hypersensitivity to the components of study medication<br>• Sorbitol intolerance or malabsorption, hereditary form of fructose intolerance |
| **Study drugs** | **Intervention (administered orally):**<br>• Givinostat oral suspension (10 mg/ml) bid after a meal, in combination with ECM, including standard CS therapy<br>• The starting dose of givinostat in the present long-term study was the same level (A, B, or C) that the patient was receiving at the end of the previous DMD givinostat study and it was adjusted for the correspondent weight category as described below:<br>– Regimen A: 20–70 mg oral givinostat bid<br>– Regimen B: 13–47 mg oral givinostat bid<br>– Regimen C: 11–37 mg oral givinostat bid<br>• For patients naïve to givinostat, treatment was started with Regimen B |
| **Concomitant medication** | **Permitted concomitant medication**: stable CS treatment; vitamin D, calcium, and any other supplements allowed if clinically indicated; testosterone, if used as a replacement therapy for the treatment of delayed puberty |


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| | |
|---|---|
| | **Prohibited concomitant medication**: any other investigational drug; any dystrophin restoration product (e.g. ataluren, eteplirsen); and use of any pharmacologic treatment, other than CS, that might have an effect on muscle strength or function (e.g. growth hormone) |
| **Primary outcomes** | Type, incidence, and severity of **treatment related**/not related **AEs** and SAEs (Baseline through week 48 and then yearly until end of study) |
| **Other outcomes used in the model/specified in scope** | • Walking ability (ambulation); **age at loss of ambulation**<br>• Muscle function (change from baseline in physical function as measured by the PUL and MFM; non-ambulant only: change in physical function from baseline in the EK score)<br>• Muscle strength (ambulant: change from baseline in knee extension and elbow flexion, as measured by HHM; non-ambulant: change in upper limbs muscle strength evaluated by HHM)<br>• Ability to undertake activities of daily living (NSAA; non-ambulant only: change in patient and/or parent/caregiver reports of activities of daily living as measured by Barthel Index)<br>• Respiratory function (change from baseline in respiratory function; e.g. FVC, FEV1, PEF, **age at non-invasive ventilation**, **age at FVC<1L**, **age at FVC<30%**<br>• Health-related quality of life (change in patient HRQoL either self-reported or proxy-reported by parent/caregiver, as measured by PedsQL for paediatric patients and by SF-36 for adult patients)<br>• Age at major disease milestones (e.g. age at loss of ambulation, age at respiratory support needed during the day, age at scoliosis surgery, age at death) |
| **Other outcomes of interest** | • PK assessments |
| **Pre-planned subgroups** | • N/A |

Outcomes listed in bold are included in the economic model.
Abbreviations: 6MWT, 6-minute walking test; AE, adverse event; bid, twice daily; CS, corticosteroids; DCO, data cut off; DMD, Duchenne muscular dystrophy; ECM, established clinical management; EK; Egen Klassifikation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HHM, hand-held myometry; HRQoL, health-related quality of life; MFF, muscle fat fraction; MFM, motor function measures; MRS, magnetic resonance spectroscopy; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; PedsQL, Pediatric Quality of Life Inventory; PEF, peak expiratory flow; PK, pharmacokinetic; PUL, Performance of Upper Limb; QTcF; Fridericia's correction; SAE, serious adverse event; SF-36, 36-Item Short Form Health Survey; UK, United Kingdom; USA, United States of America; VL, vastus lateralis.
Source: DoF (Study 51 Clinical Study Report; Dec 2023 DCO).[135]

### B.2.3.6 OLE study | Study outcomes

The primary endpoints focus on the type, incidence, and severity of treatment-related and non-related AEs and SAEs throughout the study.[139] Secondary endpoints depend on whether patients are ambulant or non-ambulant. For ambulant boys, assessments include changes from baseline in physical function (measured by the 6MWD, NSAA and timed function tests), and change from baseline in muscle strength (e.g. knee extension and elbow function), at Week 48 and then yearly until the end of study. For non-ambulant boys/young men, assessments include changes from baseline in physical function measured by the Egen Klassifikation (EK) score, patient/caregiver reports of daily living activities measured by the Barthel Index, and upper limb muscle strength measured by hand-held myometry (HHM). Additionally, performance of upper limb (PUL), motor function measures (MFMs), respiratory function, QoL, and age at major disease milestones are being assessed in both ambulant


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and non-ambulant boys/young men.[139] Exploratory endpoints comprise a comparative analysis between the delayed givinostat group and the givinostat group.[139]

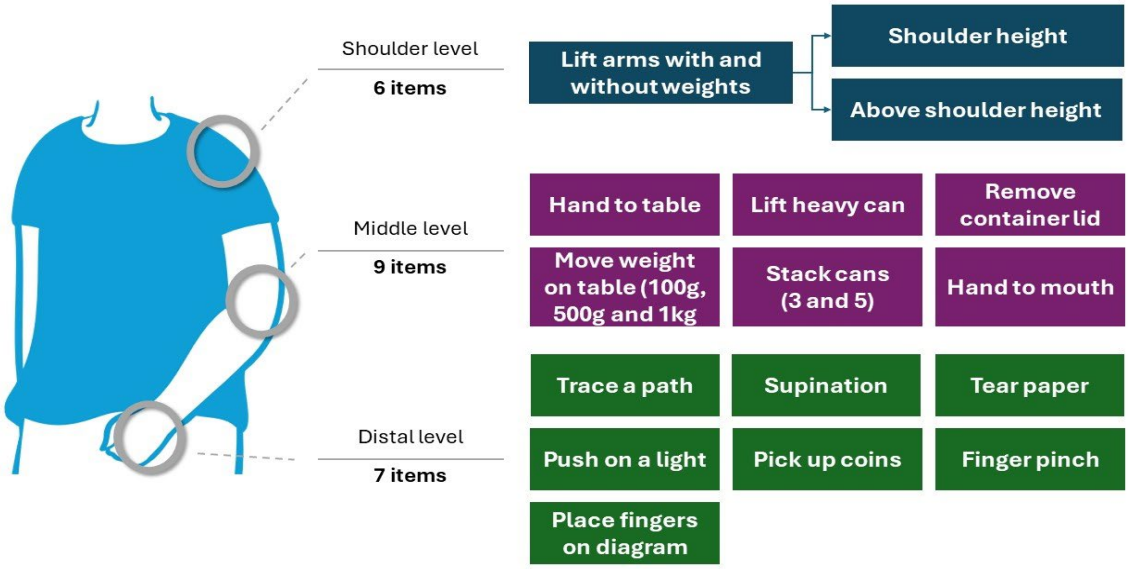
### Loss of upper limb function

The PUL test assesses upper limb function, including hand-to-mouth function, in ambulant and non-ambulant boys and young men with DMD. It comprises an entry item to define the broad starting functional level and 22 items subdivided into shoulder level (6 items, max score 12), elbow (9 items, max score 17) and distal level (7 items, max score 13) dimension (Figure 14).[169] Each domain (shoulder, elbow, distal) can be scored separately and then summed to a maximum global score of 42.

Two PUL versions are used in the OLE study: PUL version 1.2 only in the first 18 enrolled boys (rolled over from Study 43) until Month 16 and then PUL version 2.0 in all boys.[139]

Over the last few years, the PUL has been increasingly used in ambulant cohorts in clinical trials to assess early signs of upper limb involvement and as the primary measure in studies on non-ambulant patients.[170, 171]

**Figure 14: Performance of upper limb assessment (PUL) 2.0 in DMD**




Abbreviations: DMD, Duchenne muscular dystrophy.
Source: Pane et al. 2018.[169]

### Health-related quality of life

HRQoL is being assessed in the OLE study using the Pediatric Quality of Life Inventory (PedsQL) for paediatric patients and 36-item Short Form Health Survey (SF-36) for adult patients (at baseline, Week 48 and then yearly till the end of the study).[134]

The PedsQL is being completed by parents/caregivers (the Proxy Report) and by subjects (the Self-Report). The endpoints of interest are the changes from baseline in the PedsQL and PedsQL Neuromuscular Module by each dimension and Total Score (subject and


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parent/caregiver) to Week 48 and then yearly until the data cut off date.[139] Numerically higher PedsQL scores indicates better HRQoL, thus an increase in score indicates improvement in HRQoL.[139]

#### B.2.3.7 OLE study | Assessment timepoints and follow-up

Patients attend study site visits in weeks 1–4, 6, 8, 12, 16, and then every 4 months until the end of the study or early withdrawal.[134] At every visit, haematology and AE assessments are completed. Blood chemistry and ECG tests are carried out at the end of the first and second months and at each visit that follows. Coagulation tests are performed at the end of Month 2 and at each visit that follows. At each visit beginning with Week 16 (Month 4), the following are completed for all patients: urine analysis, PK blood sample collection, study drug dispensation and compliance, PUL and MFM. For ambulant patients, outcomes recorded at every visit from Week 16 comprise timed function tests, NSAA, 6MWT, knee extension, and elbow flexion muscle strength. For non-ambulant patients, outcomes recorded at every visit from Week 16 comprise physical function by EK, Barthel Index, and elbow flexion muscle strength. Pulmonary function tests are performed every 4 months for non-ambulant patients and annually for ambulant patients beginning from Week 16. Quality of life is measured, and an echocardiogram is performed at every 4-monthly visit.[134]

### *B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

#### B.2.4.1 Missing data

See Table 15 for a summary of handling of missing data.

#### B.2.4.2 EPIDYS | Statistical analyses

Statistical methods used in EPIDYS are summarised in Table 15.

**Table 15: EPIDYS | Summary of statistical analyses**

| | |
|---|---|
| **Hypothesis objective** | The study hypothesis was that givinostat in combination with ECM improved 4SC by at least 2 seconds compared with placebo in combination with ECM after 18 months of treatment<br>The null hypothesis for the primary endpoint was no difference in mean change in 4SC from baseline to 18 months between the givinostat and placebo treatment groups |
| **Statistical analysis** | All analyses done in SAS 9.4<br>**Primary endpoint statistical analyses**<br>The primary endpoint was analysed using an ANCOVA. As prespecified in the SAP, blinded 4SC data were log-transformed before analysis because they were not normally distributed. The dependent variable was log change in 4SC results from baseline to 18 months, with log 4SC, time-to-rise, time-to-run or walk 10 metres, and 6MWT as baseline covariates, and randomised treatment, CS use, and age as independent class variables<br>**Analysis of key secondary endpoints**<br>Key secondary endpoints (change from baseline after 18 months in NSAA total score, NSAA cumulative loss of function, TTRF, 6MWT, knee extension, elbow flexion, and VL MFF) were analysed using a similar |


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ANCOVA (without log transformation), except for NSAA cumulative loss of function, which was analysed using negative binomial regression

**Hochberg procedure**

The key secondary endpoints were prospectively adjusted for multiplicity using the Hochberg procedure, because they were of equal clinical relevance. In this procedure, p-values are ordered from least to most significant: if the largest one-sided p-value is ≤0.025 then all endpoints are significant; otherwise, the endpoint with the largest p-value is deemed non-significant and the next largest p-value is considered in relation to 0.025/2 = 0.0125. If the nth ordered one-sided p-value reaches ≤0.025/n, treatment effects for that and subsequent endpoints are significant; otherwise, the nth p-value is deemed nonsignificant. As the Hochberg procedure does not account for correlation between endpoints, a *post hoc* permutation test was also done to assess the overall probability of efficacy while accounting for this correlation

**Other endpoints**

The binary efficacy variables (proportion of boys with >10% persistent worsening in 6MWT, proportion of boys losing ambulation during the study) were analysed using logistic regression. Baseline values for: 4SC, TTRF, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose (in years and months), were included as independent covariates. Randomised treatment group and concomitant corticosteroid use were included as independent classification factors

The time to event variables (time to 10% persistent worsening in 6MWT, time to persistent loss of standing) were analysed using Cox proportional hazards modelling

Where adjustment of alpha was applied to any of the above analyses, the 2-sided CIs were adjusted as below

| Analysis timepoint | Endpoint | Applicable p-value (1-sided) | Applicable p-value (2-sided) | CI (2-sided) |
|---|---|---|---|---|
| Final analysis | 4SC at 18 months in the Target ITT population | p≤0.025 | p≤0.05 | 95% |
| | Key secondary efficacy endpoints at 18 months in the Target ITT population | p≤0.025/i (i=rank according to Hochberg procedure) | p≤0.05/i (i=rank according to Hochberg procedure) | 100(1−0.05/i)% (i=rank according to Hochberg procedure) |
| General | All other analysis (supportive only) | p≤0.025 (nominal p-values presented) | p≤0.05 (nominal p-values presented) | 95% |

Safety data were prespecified to be analysed descriptively only

**Sample size, power calculation**

**Original sample size calculation, and blinded interim futility analysis**

The sample size was originally calculated to provide 90% power and a 1-sided alpha of 2.5% to detect a true difference of 3 seconds between givinostat and placebo in the Target ITT (Group A) for 4SC 18 month change from baseline, assuming a common SD of 6 seconds. The estimated SD was based on publicly available Phase 3 study data on ataluren and drisapersen in patients with DMD, in addition to sponsor's data. A pre-planned interim analysis was performed in January 2020 by an independent statistician, after the first 50 boys completed 12 months of treatment. At this interim futility analysis, there was no efficacy assessment, no unblinded analysis of the primary endpoint or early stopping of the study for efficacy and, hence, no alpha spent. The futility analysis was based on MRS VL MFF data at 12 months, with LS means obtained from an ANCOVA model on change from baseline at the respective visit with baseline value and age fitted as covariates, and


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| | |
|---|---|
| | concomitant corticosteroid use and treatment group as independent classification factors. The futility analysis was blinded to the sponsor, and unblinded for the IDMC; the IDMC only communicated to the sponsor whether the study should proceed or be stopped, based on whether the study had met the futility criteria. Futility was considered if the mean change in VL MFF in the givinostat group was equal to or worse (i.e. higher) than that seen in the placebo group. The LS means were 3.61 and 7.95 for givinostat and placebo, respectively, so futility was not met, and the trial continued with a pre-planned blinded sample size re-assessment allowing for a sample size reduction without affecting study power. No other changes to the study conduct were made because of this analysis and there was no bias adjustment<br>**Subsequent sample size calculation**<br>Based on an SD of 3.094 seconds in the masked sample size reassessment (approximately half of that assumed in the original power calculation), 102 boys would provide 90% power, with a one-sided alpha of 2.5%, to detect a difference of 2 seconds in the results of the 4SC between the givinostat and placebo groups at 18 months in the Target ITT (2 second difference confirmed as clinically relevant based on analyses by Wong et al., and substantiated by data from the CINRG natural history database). With an estimated drop-out of 8%, 110 boys were needed in the Target ITT (Group A) and up to 50 (35% of the Overall ITT population) needed for Group B |
| **Data management, patient withdrawals** | **Handling of missing data**<br>Any missing values classified as 1 (due to reasons other than being non-ambulatory or physically unable to perform the test/assessment; included missing data due to COVID-19) were imputed using the mean of all non-missing values for the respective measurement and timepoint across all boys randomised to the respective treatment and in the respective concomitant corticosteroid stratum and group (i.e. Target ITT or Group B). Any missing values classified as 2 (due to being either non-ambulatory or otherwise physically unable to perform the test/assessment; i.e. disease progression) were imputed by setting the value to 0 or to twice the maximum non-missing value recorded across all boys depending on the directionally of the test. In all cases, imputation of any data classified as 1 were completed first, followed by imputation of any data classified as 2<br>For the NSAA assessment, where the total score is a sum of ordinal item scores, for imputation of Class 1 missing data, each item score was imputed using the mode of the non-missing scores for the same item and visit across all boys randomised to the same treatment and in the same concomitant corticosteroid stratum and group. If the assessment was attempted and ≤8 were missing, then the missing item scores were imputed using the mode of the non-missing item scores for the boy and visit. If ≥9 items were missing, then the missing item scores for that boy at that visit were imputed as zero. In the event of missing values classified as 2, all item scores and the total score were imputed to zero<br>**Handling of missing data due to patient withdrawals**<br>Missing data at any scheduled timepoint were imputed according to the above rules, including any scheduled timepoints after a boy withdrew early. In these cases, where the final assessment prior to withdrawal was missing and determined to be Class 2 missing data, all missing assessments post withdrawal were also considered Class 2. Otherwise, these were considered Class 1. Where this applied to an NSAA assessment, Class 1 referred to the scenario where 'Was assessment attempted?' = No. Where a date of assessment was required, the predicted date for imputed timepoints post withdrawal was used. The same approach was followed for any completely missing visits prior to withdrawal or completing the study, where no information had been entered into the |


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| | |
|---|---|
| | respective CRF assessment page indicating whether it was performed. Where data entered into the CRF for an assessment were ambiguous such that they do not reflect any of the expected responses outlined above and therefore missing data could not be classified, a worst-case approach was followed and the missing data was assumed Class 2. Cases where data entered into the CRF assessment page which comply with the responses outlined above but additional information was available to contradict the classification were assessed on a case-by-case basis to determine the appropriate classification to be applied |
| **Statistical analysis timepoints** | Boys were enrolled between 6 June 2017 and 22 Feb 2022<br>A pre-planned interim futility analysis was performed on 20 January 2020 as described above. Blinded sample size reassessment followed this analysis<br>Formal analyses were conducted in the Target ITT population for the primary efficacy endpoint and all key secondary efficacy endpoints at 18 months |

Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walking test; ANCOVA, Analysis of covariance; CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; CRF, case report form; DMD, Duchenne muscular dystrophy; ECM, established clinical management; IDMC, Independent data monitoring committee; IRT, interactive response technology; ITT, intention-to-treat; LS, least squares; MFF, muscle fat fraction; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; N, number; NSAA, North Star Ambulatory Assessment; PODCI, Paediatric Outcomes Data Collection Instrument; SD, standard deviation; TTRF, time to rise from the floor; VL, vastus lateralis.
Source: Mercuri et al. 2024;[22, 132] EPIDYS CSR (2022);[136] EPIDYS SAP (2022).[148]

### B.2.4.3 EPIDYS | Analysis sets

The analysis sets and their definitions are described in Table 16. The Target ITT population (Group A) included all boys with baseline MRS VL MFF >5% to 30%; this population was used for the prespecified efficacy analyses.[22, 132] The Overall ITT population (also referred to as the Safety population) was used for safety evaluations and *post hoc* supportive efficacy analyses.[22, 132] As the efficacy results are consistent between the Overall ITT population and the Target ITT (Group A) population (Section B.2.6.4),[22, 132] the efficacy results from the Overall ITT population are used to inform the CEM, to use the largest population for which efficacy data are available.

**Table 16: EPIDYS | Analysis sets for the Overall ITT and Target ITT population**

| Analysis set | Definition | Givinostat (n) | Placebo (n) |
|---|---|---|---|
| **Overall ITT population (Safety population)** | All randomly assigned boys who received ≥1 dose of study drug, and had ≥1 non-missing post-baseline 4SC measure or missing post-baseline 4SC measure due to being either non-ambulatory or otherwise physically unable to take part in the assessment, with treatment group assignment according to initial randomisation; used for safety evaluations and *post hoc* supportive efficacy analyses | 118 | 61 |
| **Target ITT population (Group A)** | All boys with baseline MRS VL MFF >5% to 30% (comprised boys not at risk of sudden, complete loss of ambulation, but expected to show decline in the study endpoints over 18 months); used for the prespecified efficacy analyses | 81 | 39 |


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| | | | |
|---|---|---|---|
| **Off-target ITT population (Group B)** | MRS VL MFF of ≤5%, or >30%; recruited so that the safety of givinostat could be evaluated in a broader population of boys with DMD | 37 | 22 |
| **PK analysis set for the Target population** | All boys in the Target ITT population who received ≥1 dose of treatment with givinostat and who had ≥1 post-dose concentration of study drug; used for all formal PK summaries and analyses | 80 | 0 |
| **PK analysis set for the Overall population** | All boys in Groups A and B who received ≥1 dose of treatment with givinostat and who had ≥1 post-dose concentration of study drug; used for any supportive PK evaluations. Final membership of the PK analysis set in both the Target and Overall populations was confirmed after unblinding | 117 | 0 |
| **MRS cohort** | All randomly assigned boys in the Target ITT population who completed at least one post-baseline assessment; used for the VL MFF analyses. | 77 | 37 |

Abbreviations: ITT, intention-to-treat; MFF, muscle fat fraction; MRS, magnetic resonance spectroscopy; n, number; N/A, not applicable; PK, pharmacokinetic; VL, vastus lateralis.
Source: Mercuri et al. 2024;[22, 132] EPIDYS CSR (2022).[136]

### B.2.4.4 EPIDYS | Patient flow

Between 6 June 2017 and 22 February 2022, 359 boys were assessed for eligibility, 179 of whom were enrolled into EPIDYS. All 179 boys were randomly assigned to receive either givinostat (n=118) or placebo (n=61), and 170 (95%) completed the study. Based on MRS VL MFF, 120 (67%) of the 179 boys were in the Target ITT population (114 [95%] completed the study) and 59 (33%) were in Group B (56 [95%] completed the study. For full details of patient flow in EPIDYS, see Appendix D.4

### B.2.4.5 EPIDYS | Patient baseline characteristics

Baseline demographic and disease characteristics were similar in the givinostat and placebo groups, for both the Overall ITT population and for the Target ITT (Group A) (Table 17).[22, 132] In the Target ITT population, the mean age of boys was 9.6 years in the givinostat group, and 9.8 years in the placebo group, and the mean time since diagnosis was 5.7 and 5.6 years, respectively.[136] Most boys in the Target ITT population had deletion type of DMD mutations (72% in both treatment groups).[22, 132] Deflazacort was the most common corticosteroid and most boys in both groups were receiving CS daily.[22, 132]


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**Table 17: EPIDYS | Patient baseline demographics and disease characteristics**

| Characteristic | Overall ITT population | | Target ITT population | |
|---|---|---|---|---|
| | Givinostat* n=118 | Placebo* n=61 | Givinostat* n=81 | Placebo* n=39 |
| **Age, years** | 9.8 (2.0) | 10.0 (2.1) | 9.6 (1.9) | 9.8 (2.1) |
| **Race†** | | | | |
| **White** | 106 (90) | 57 (93) | 74 (91) | 36 (92) |
| **Asian** | 4 (3) | 2 (3) | 3 (4) | 1 (3) |
| **Black** | 3 (3) | 0 | 0 | 0 |
| **Other** | 5 (4) | 2 (3) | 4 (5) | 2 (5) |
| **BMI, kg/m$^2$** | 19.7 (4.10): 12.4–30.6 | 19.9 (4.40): 13.3–31.4 | 19.5 (3.83) 12.4–30.6 | 20.1 (4.52): 13.3–31.3 |
| **Weight, kg** | 31.2 (8.9) | 32.6 (10.8) | 30.2 (7.1) | 31.8 (9.6) |
| **Time since diagnosis, years** | 5.5 (2.6) | 5.6 (2.7) | 5.7 (2.5) | 5.6 (2.9) |
| **Dystrophin mutation** | | | | |
| **Deletion** | 83 (70) | 40 (66) | 58 (72) | 28 (72) |
| **Duplication** | 17 (14) | 14 (23) | 13 (16) | 9 (23) |
| **Point mutation** | 18 (15) | 7 (11) | 10 (12) | 2 (5) |
| **Time since corticosteroid initiation (years)** | 3.6 (2.1) | 4.0 (2.1) | 3.7 (2.1) | 3.8 (2.1) |
| **Type of corticosteroid, n (%)** | | | | |
| **Prednisone** | 20 (16.9) | 15 (24.6) | 10 (12.3) | 10 (25.6) |
| **Deflazacort** | 91 (77.1) | 45 (73.8) | 66 (81.5) | 29 (74.4) |
| **Other** | 7 (5.9) | 1 (1.6) | 5 (6.2) | 0 |
| **Corticosteroid schedule, n (%)** | | | | |
| **Daily** | 99 (83.9) | 48 (78.7) | 69 (85.2) | 31 (79.5) |
| **Intermittent** | 19 (16.1) | 13 (21.3) | 12 (14.8) | 8 (20.9) |

Data are median (IQR), n (%), or mean (SD); range. The Target ITT population was used for the prespecified efficacy analyses; supportive efficacy analyses were conducted *post hoc* in the Overall ITT population, which was also used for the safety evaluations; all boys were also receiving systemic corticosteroids, in a dose and regimen that was to remain unchanged over the follow-up period; †race was self-reported.
Abbreviations: BMI, body mass index; IQR, interquartile range; ITT, intention-to-treat; n, number; SD, standard deviation.
Source: Mercuri et al. 2024.[22, 132]; EPIDYS CSR (2022).[136]

### B.2.4.6 OLE study | Statistical analyses

Statistical methods used in OLE study are summarised in Table 18.


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**Table 18: Ongoing OLE study | Summary of statistical analyses**

| | |
|---|---|
| **Hypothesis objective** | No formal statistical hypothesis testing is conducted for the study<br>The null hypothesis for exploratory comparisons is that 'givinostat' and 'delayed givinostat' are equivalent |
| **Statistical analysis** | All analyses are done in SAS.9.4<br>In each interim analysis, all safety and selected efficacy variables are analysed<br>**Primary safety analysis**<br>The primary endpoint is the type, incidence and severity of treatment related/not related AEs and SAEs, including those that lead to discontinuation, from baseline through to Week 48 and then yearly until the end of the study/cut-off date. Safety data are evaluated descriptively based on the Safety population and AE data are coded using the MedDRA dictionary, presented by System Organ Class<br>**Secondary safety analysis**<br>Summary statistics are presented for changes in vital signs, weight, height and BMI, and in ECG and ECHO parameters. Laboratory test values are summarised similarly<br>**Secondary efficacy analysis**<br>All secondary efficacy analyses are performed on the ITT population<br>**Exploratory efficacy analysis comparing 'delayed givinostat group' vs. 'givinostat group'**<br>The 'change from baseline' endpoints are analysed using repeated measures model on change from baseline at each timepoint with baseline value, age at first dose, concomitant steroid use, treatment group and visit as fixed effects. An unstructured covariance matrix is used. LS means are estimated and treatment effects are presented with nominal 95% CI and p-values<br>For the endpoints also analysed in EPIDYS, data are either log transformed or not in alignment with the core study conclusions. The need to apply a log transformation to the remaining endpoints is assessed by examining the model residuals from a model without a treatment effect term after the final database lock. Back transformation is applied for presentation of results and presentation is amended<br>The 'time to event' endpoints are analysed with Cox Proportional Hazards models, with treatment group and concomitant steroid use as class variables and age at first dose as a covariate. The HR (givinostat: delayed givinostat) is presented along with nominal 95% CI and p-value. Boys not reaching a disease milestone are censored on the last date known to be on study. Tests for proportional hazards are performed by examining the log-log Kaplan–Meier estimates over time and evaluating whether the curves are reasonably parallel. In the event of non-proportional hazards, output(s) should be interpreted with caution. A mixed effect random coefficient analysis is used to fit the dependent variables against age, where age will be treated as a random effect, 'treatment group' as fixed effect, treatment by age as interaction term and a random intercept fitted. An unstructured covariance matrix is used<br>Pulmonary function tests and physical function tests (6MWT, NSAA, 4SC, time to walk 10 m, TTRF) are analysed using a mixed effect random coefficient analysis. The need to apply a log transformation to endpoints before analysis is assessed after final database lock by examining the residuals from a model without a treatment effect term. Back transformation is applied in case for presentation of results and presentation is amended |


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| | |
|---|---|
| | **Pharmacokinetic analysis**<br>PK results are analysed with pop PK model to continue the PK assessment of givinostat |
| **Sample size, power calculation** | No sample size and power considerations are applicable |
| **Data management, patient withdrawals** | **Handling of dropouts or missing data**<br>For the efficacy analyses, any missing data for continuous values for a participant are classified as follows:<br>• (1) The participant has missing data for reasons other than being non-ambulatory or physically unable to perform the test/assessment<br>• (2) The participant has missing data due to being non-ambulatory or otherwise physically unable to perform the test/assessment<br>Any missing values classified as 1 are imputed using the mean (or mode) of all non-missing values for the respective measurement and time point across all relevant subjects in the treatment group<br>Any missing values classified as 2 are imputed by setting the value to zero or to twice the maximum non-missing value across all subjects depending on the directionality of the test, if not otherwise specified in the SAP.<br>Boys who lose ambulation after baseline have the results subsequent to the loss of ambulation imputed to worst case (Class 2)<br>Missing data at completely missing visits prior to withdrawal or completing the study, or missing data where the visit was completed but the data is missing, are imputed according to the following rules: where the final assessment prior to skipped assessment is missing and determined to be Class 2 missing data, all missing assessments between the performed visits are also considered Class 2. Otherwise, they are considered Class 1.<br>In all cases, imputation of any data classified as 1 is completed first, followed by imputation of any data classified as 2 |
| **Statistical analysis timepoints** | Enrolment began 25 October 2017. The study is ongoing. Interim analyses were conducted on 30 November 2018, 15 November 2019, 31 December 2020, 31 December 2021 and 31 December 2023 (the data cut presented here). The first three interim analyses reported all subjects in one group (givinostat) because the blind was maintained in parent studies which were ongoing. For the subsequent interim analyses, all safety data and efficacy variables were analysed |

Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walking test; AE, adverse event; BMI, body mass index; CI, confidence interval; DCO, data cut off; ECG, electrocardiogram; ECHO, echocardiogram; HR, hazard ratio; ITT, intention-to-treat; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; PK, pharmacokinetic; SAE, serious AE; SAP, statistical analysis plan; TTRF, time to rise from the floor.
Source: DoF (Study 51 Clinical Study Report; Dec 2023 DCO);[135] DoF (Study 51 Protocol).[134]

### B.2.4.7 OLE study | Analysis sets

The analysis sets and their definitions are described in Table 19. The three treatment groups are described in B.2.3.5.


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**Table 19: OLE study | Analysis sets (Dec 2023 DCO)**

| Analysis set | Definition | Givinostat group | Delayed givinostat group | Naïve givinostat group | Overall |
|---|---|---|---|---|---|
| **Enrolled set** | All boys who passed screening in this study irrespective of whether or not they received the study treatment prior to the screening | 119 | 58 | 30 | 207 |
| **Safety analysis set (SAS)** | All boys who took ≥1 dose of givinostat in this study | 119 | 58 | 30 | 207 |
| **ITT set** | All boys who took ≥1 dose of givinostat in this study and who had ≥1 post-baseline efficacy measurement, irrespective of any deviation from the protocol or premature discontinuation | 119 | 58 | 30 | 207 |
| **PK analysis set** | All boys who took ≥1 dose of givinostat in this study and who had ≥1 pharmacokinetic concentration, irrespective of any deviation from the protocol or premature discontinuation | 116 | 57 | 30 | 203 |

Abbreviations: DCO, data cut off; ITT, intention-to-treat; OLE, open-label extension; PK, pharmacokinetic; SAS, Safety analysis set.
Source: DoF (Study 51 Clinical Study Report; Dec 2023 DCO).[135]


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### B.2.4.8 OLE study patient flow

At the DCO of 31 December 2023, enrolment was ongoing; 194 boys were screened and enrolled in the study.[135] Twenty-one boys had prematurely discontinued from the study (7 for withdrawn consent, 8 due to AEs, and 2 lost to follow-up and 4 due to other reasons). The mean study duration was 1,204.2 days (SD ±446.3; median 1,179.0 [range 99 to 2,259] days). No boys/young men had completed the study as of 31 December 2023.[135]

The 207 enrolled boys fell into three groups: the givinostat group (n=119), the delayed givinostat group (n=58) and the naïve givinostat group (n=30), see Section B.2.3.5 for definitions.[135]

### B.2.4.9 OLE study | Patient baseline characteristics

Baseline demographic and disease characteristics were similar across the givinostat and the delayed givinostat groups, while the naïve givinostat group were a little younger, lighter, had taken CS for less time, were all ambulant at screening, and were a little less likely to be of White race (Table 20).[135] There were 12 (5.8%) non-ambulant boys; 9 in the givinostat group and 3 in the delayed givinostat group. Mean age overall was 11.5 years (range 6.2 to 17.6 years) and 10.5 years in the naïve givinostat group). All boys/young men were on corticosteroid treatment and the mean time since corticosteroid initiation was 5.4 years overall (range 0.9 to 12.6 years) and 4.5 years in the naïve givinostat group. All boys were using CS as per the protocol. The most frequently used medications, excluding CS, were paracetamol (58.0%), Vitamin D and analogues (colecalciferol [40.6%] and ergocalciferol [33.8%]), and ibuprofen (31.4%).[135]


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**Table 20: OLE study | Patient baseline demographics and disease characteristics (SAS)**

| Characteristic | Givinostat group N=119 | Delayed givinostat group N=58 | Naïve givinostat group N=30 | Overall N=207 |
|---|---|---|---|---|
| **Age, years** | 11.7 (2.1) | 11.5 (2.1) | 10.5 (2.3) | 11.5 (2.1) |
| **Race, n (%)** | | | | |
| **White** | 109 (91.6) | 54 (93.1) | 23 (76.7) | 186 (89.9) |
| **Asian** | 2 (1.7) | 2 (3.4) | 2 (6.7) | 6 (2.9) |
| **Black or African American** | 4 (3.4) | 0 | 1 (3.3) | 5 (2.4) |
| **Other** | 4 (3.4) | 2 (3.4) | 4 (13.3) | 10 (4.8) |
| **BMI at screening, kg/m$^2$** | 20.9 (5.0) | 21.3 (5.2) | 20.2 (4.0) | 20.9 (5.0) |
| **Weight at screening, kg** | 35.7 (10.9) | 37.3 (12.1) | 32.4 (9.6) | 35.7 (11.1) |
| **Ambulant status at screening, n (%)** | | | | |
| **Ambulant** | 110 (92.4) | 55 (94.8) | 30 (100.0) | 195 (94.2) |
| **Non-ambulant** | 9 (7.6) | 3 (5.2) | 0 | 12 (5.8) |
| **Time since diagnosis, years** | 7.6 (2.5) | 7.3 (2.7) | 6.9 (2.7) | 7.4 (2.6) |
| **DMD mutation, n (%)** | | | | |
| **Deletion** | 80 (67.2) | 38 (65.5) | 18 (60.0) | 136 (65.7) |
| **Duplication** | 17 (14.3) | 13 (22.4) | 6 (20.0) | 36 (17.4) |
| **Point mutation** | 19 (16.0) | 5 (8.6) | 4 (13.3) | 28 (13.5) |
| **Other** | 3 (2.5) | 2 (3.4) | 2 (6.7) | 7 (3.4) |
| **Time since corticosteroid initiation (years)** | 5.7 (2.4) | 5.4 (2.3) | 4.5 (2.7) | 5.4 (2.4) |
| **Type of corticosteroid, n (%)** | | | | |
| **Prednisone** | 16 (13.4) | 15 (25.9) | 3 (10.0) | 34 (16.4) |
| **Deflazacort** | 99 (83.2) | 42 (72.4) | 27 (90.0) | 168 (81.2) |
| **Other** | 4 (3.4) | 1 (1.7) | 0 | 5 (2.4) |
| **Corticosteroid schedule, n (%)** | | | | |
| **Daily** | 93 (78.2) | 45 (77.6) | 28 (93.3) | 166 (80.2) |
| **Intermittent** | 26 (21.8) | 13 (22.4) | 2 (6.7) | 41 (19.8) |

Data are mean (SD); N = the number of boys in the analysis set; n = the number of boys meeting the criterion; (%) = n/N*100. Arm span is used in place of height when deriving body mass index for non-ambulant boys/young men

Abbreviations: BMI, body mass index; DCO, data cut off; OLE, open-label extension; SAS, Safety analysis set.. SD, standard deviation.

Source: DoF (Study 51 Clinical Study Report; Dec 2023 DCO).[135]


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### *B.2.5 Quality assessment of the relevant clinical effectiveness evidence*

Quality assessment of EPIDYS is provided in Appendix D.1.4.3, based on Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). A discussion around the strengths and limitations of EPIDYS is provided in Section B.2.12.

Quality assessment of the OLE study is provided in Appendix D.1.4.3, based on NICE process and methods [PMG24] Section 2.5.


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## *B.2.6 Clinical effectiveness | Ambulant boys*

This section presents the available givinostat efficacy data for ambulant boys with DMD from the givinostat studies:

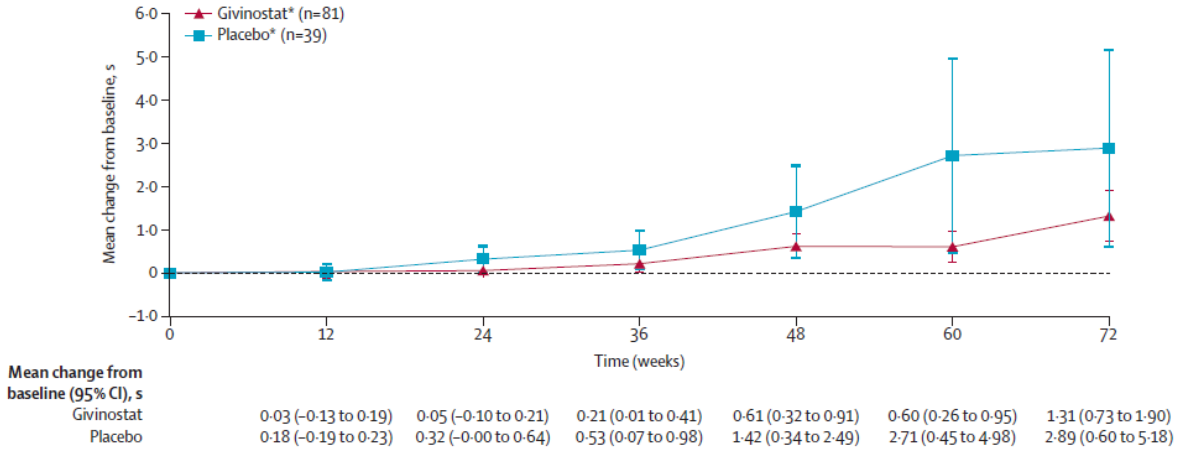
- Firstly, data from the Target ITT population (Group A) of the completed Phase 3 EPIDYS study are presented (see Section B.2.4.3 for definitions of the EPIDYS study populations)
- This is followed by a *post hoc* analysis of givinostat efficacy in the EPIDYS Overall ITT population (Section B.2.6.4)
- Then longer-term data from the December 2023 DCO of the ongoing OLE study are presented (Section B.2.6.6).

### B.2.6.1 EPIDYS | Primary endpoint | Change in 4SC | Target ITT population

There was a meaningful and statistically significant difference in the mean change in time to climb four stairs (4SC) at 18 months.[22, 132] The primary analysis of the study's primary endpoint was met with a treatment effect observed of 0.86 (p=0.035).[22, 132] The pre-specified geometric LS mean ratios for the log transformed 4SC results at 18 months versus baseline were 1.27 (95% CI 1.17 to 1.37) in the givinostat group versus 1.48 (95% CI 1.32 to 1.66) in the placebo group (ratio 0.86; 95% CI 0.75 to 0.99, p=0.035; Figure 17 and Table 21).[22, 132]

The greater worsening in 4SC results with placebo than with givinostat was apparent from Week 48 (mean changes from baseline: givinostat, ranging between 0.60 and 1.31 seconds; placebo, 1.42 to 2.89 seconds; Figure 15).[22, 132] When analysed as velocity, 4SC results at 18 months were 0.243 tasks per second in the givinostat group and 0.209 tasks per second in the placebo group, a LS mean difference of 0.034 (95% CI 0.004 to 0.065) tasks per second (p=0.029).[22, 132]

**Figure 15: Mean change of the 4SC assessment between baseline and 18 months | Target ITT population**




Data are mean (95% CI); the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 3.39 seconds for the givinostat group and 3.48 seconds for the placebo group; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC, 4-stair climb; CI, confidence interval; ITT, intention-to-treat; LS, least squares; n, number; s, seconds.
Source: Mercuri et al. 2024.[22, 132]


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**Table 21: Analysis of 4SC, change from baseline at 18 months | Target ITT population**

| Statistics | Givinostat* (N=81) | Placebo* (N=39) |
|---|---|---|
| **Log transformation applied** | | |
| Number of boys included in analysis, n (%) | 81 (100) | 39 (100) |
| GLS mean | 1.27 | 1.48 |
| 95% CI for GLS mean | 1.17, 1.37 | 1.32, 1.66 |
| GLS mean ratio (givinostat/placebo) | 0.86 | |
| 95% CI for GLS mean ratio | 0.75, 0.99 | |
| p-value | 0.034 | |
| **No log transformation applied** | | |
| Number of boys included in analysis, n (%) | 81 (100) | 39 (100) |
| LS mean | 1.25 | 3.03 |
| 95% CI for LS mean | 0.31, 2.18 | 1.67, 4.39 |
| Difference in LS means (givinostat-placebo) | -1.78 | |
| 95% CI for difference in LS means | -3.46, -0.11 | |
| p-value | 0.037 | |

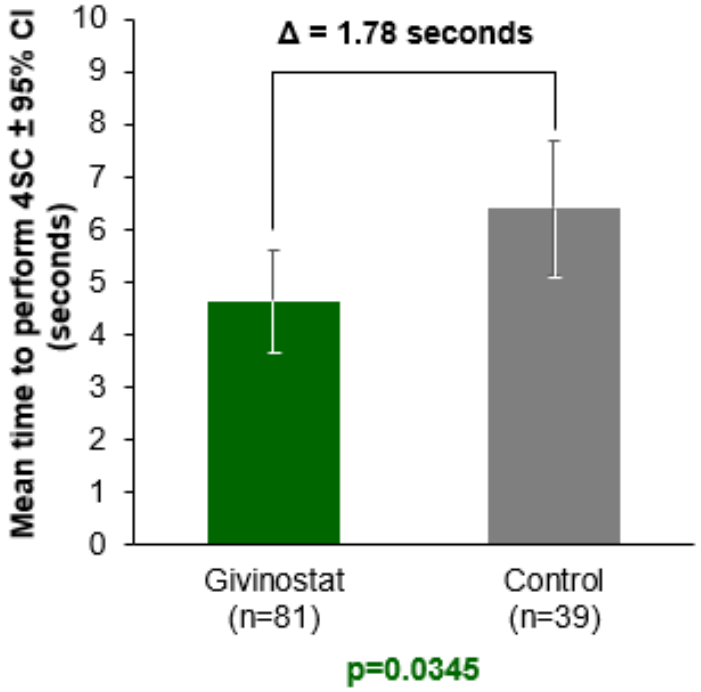
*All boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC, 4 stair-climb; CI, confidence interval; CS, corticosteroids; EOS, end of study; GLS, generalised least square; ITT, intention-to-treat population; LS: least square; N: number of boys in the study population; n: number of boys meeting the criterion.
Source: Mercuri et al. 2024.[22, 132]

### Non-log-transformed data showed a reduction of ~40% in the decline in 4SC over 18 months for givinostat vs. placebo

As 4SC is a time-based assessment, an analysis of non-log-transformed data was also carried out, to make the outcomes easier to understand. Results of this analysis showed a treatment effect (change from baseline, givinostat minus control group) of 1.78 seconds, demonstrating a slower statistically significant decline. Using non-log-transformed data at 18 months, mean 4SC changes from baseline were 1.25 seconds (95% CI 0.31 to 2.18) in the givinostat group compared with 3.03 seconds (95% CI 1.67 to 4.39) in the placebo group (LS mean difference –1.78 seconds; 95% CI –3.46 to –0.11; p=0.037; Table 21 and Figure 16).[22, 132] This translates to a reduction of approximately 40% in the decline in the 4SC over a period of 18 months compared with the placebo group. Furthermore, a benefit of 1.78 seconds shorter 4SC adds up considerably across a day to have a large impact across a boy's daily life.


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**Figure 16: Geometric LS mean change from baseline in time to perform 4SC at 18 months (non-log transformed) | Target ITT population**




Data are mean (95% CI); the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 3·39 seconds for the givinostat group and 3·48 seconds for the placebo group; *all boys were also receiving established clinical management, including systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period
Abbreviations: 4SC, 4-stair climb; CI, confidence interval; LS, least squares; ITT, intention-to-treat, n, number.
Source: Mercuri et al. 2024.[22, 132]

**Improvements in the rate of 4SC decline were consistent when adjusting for changes in the dose of givinostat**

Boys received a flexible-dose givinostat regimen, aimed at maximising efficacy, and starting with a high dose that was reduced if treatment was not tolerated. The protocol was amended to lower the starting dose, but the *post hoc* analysis of covariance (ANCOVA) suggested that the treatment effect was not affected by the change in treatment regimen (see Appendix Table 23 in Appendix E.2.1).[22, 132]

The results considering no shift of the 'tipping point' sensitivity analysis to account for missing data (see Table11 in Appendix D.2.2.1 for rationale and approaches) for the primary outcome at 18 months were similar to those obtained in the primary 4SC analysis.[22, 132]


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The company has conducted several additional analyses of EPIDYS data to determine whether dose changes affected the trial results. These confirm that changing the flexible dose regimen during the study did not affect the interpretability of the final study efficacy results and that the givinostat treatment effect was demonstrated independently of the received treatment dose.[172]

**Improvements in 4SC with givinostat compared with ECM are clinically meaningful**

The significantly smaller decline in 4SC over 18 months with givinostat versus placebo is considered to be clinically meaningful to patients, because slower 4SC correlates with reduced participation in physical and social activities in daily life and predicts loss of stair-climbing ability and ambulatory capacity.[151] A recent publication has shown that 4SC >6.2 seconds is predictive of loss of function in the following year.[161] At the end of EPIDYS, 12.3% of boys had a 4SC >6.2 seconds in the givinostat group compared with 26.5% in the placebo group. Moreover, the velocity difference between the givinostat and placebo groups of 0.034 tasks per second[22, 132] is similar to the minimal clinically important difference reported by Duong and colleagues (0.035 tasks per second; derived using a questionnaire-anchored approach).[154] The effect of givinostat treatment on clinical endpoints versus ECM is explored in the comparative efficacy section (Section B.2.8).

As the treatment effect is at least one-third of the SD of the endpoint (4SC) at baseline, and at least one-third of the SD of the 4SC baselined standard error of measurement, the minimal clinically important difference was demonstrated.[22, 132]

### B.2.6.2 EPIDYS | Key secondary endpoints | Target ITT population

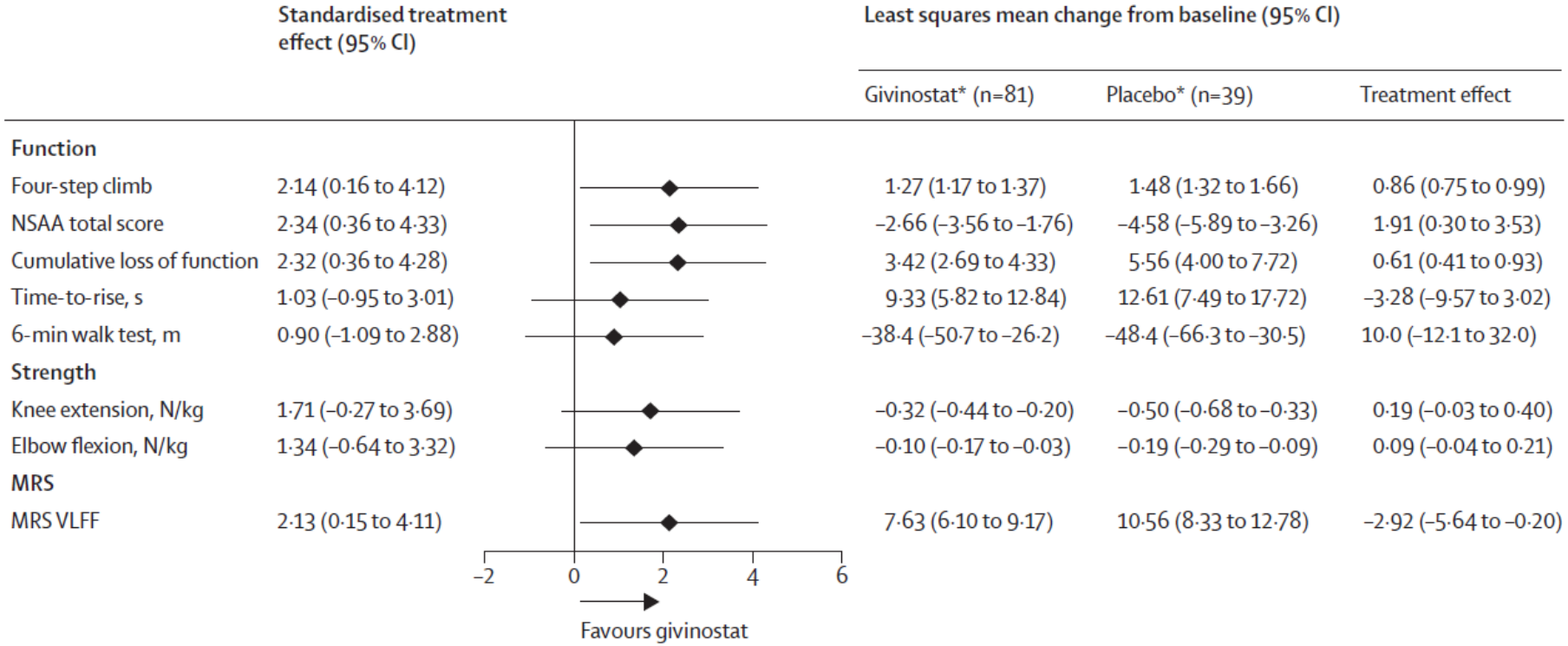
Secondary outpoint endpoints (i.e. physical function scores, muscle strength scores, and MRS assessment) were consistent with the primary 4SC outcome, demonstrating that givinostat impacts the trajectory of the disease and slows muscle mass decline compared with the control group.[22, 132]

Given the challenges of powering clinical trials in rare diseases, EPIDYS was designed and powered for the primary endpoint of 4SC.[22, 132] As described in Table 15, the key secondary endpoints were prospectively adjusted for multiplicity using the Hochberg procedure.[22, 132] After this multiplicity adjustment givinostat was numerically superior to placebo in terms of the decrease in NSAA total score from baseline, cumulative loss of function, and change from baseline in time-to-rise from the floor (see Figure 17).[22, 132] The lack of formal statistical significance for the secondary endpoints does not imply an absence of effect; but is indicative of the statistical stringency of the Hochberg adjustment procedure, which does not account for correlations between related endpoints.[22, 132]

A *post hoc* permutation test (another statistical approach to account for multiplicity) was done to assess the overall probability of efficacy while accounting for this correlation. This showed that the probability of observing the overall constellation of results under the null hypothesis of no true treatment effect was less than 0.01%, meaning that the positive results seen were highly unlikely to have happened by chance (Appendix M.5.1).[22, 132]


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**Figure 17: Forest plot of primary and secondary EPIDYS endpoints at 18 months | Target ITT population**



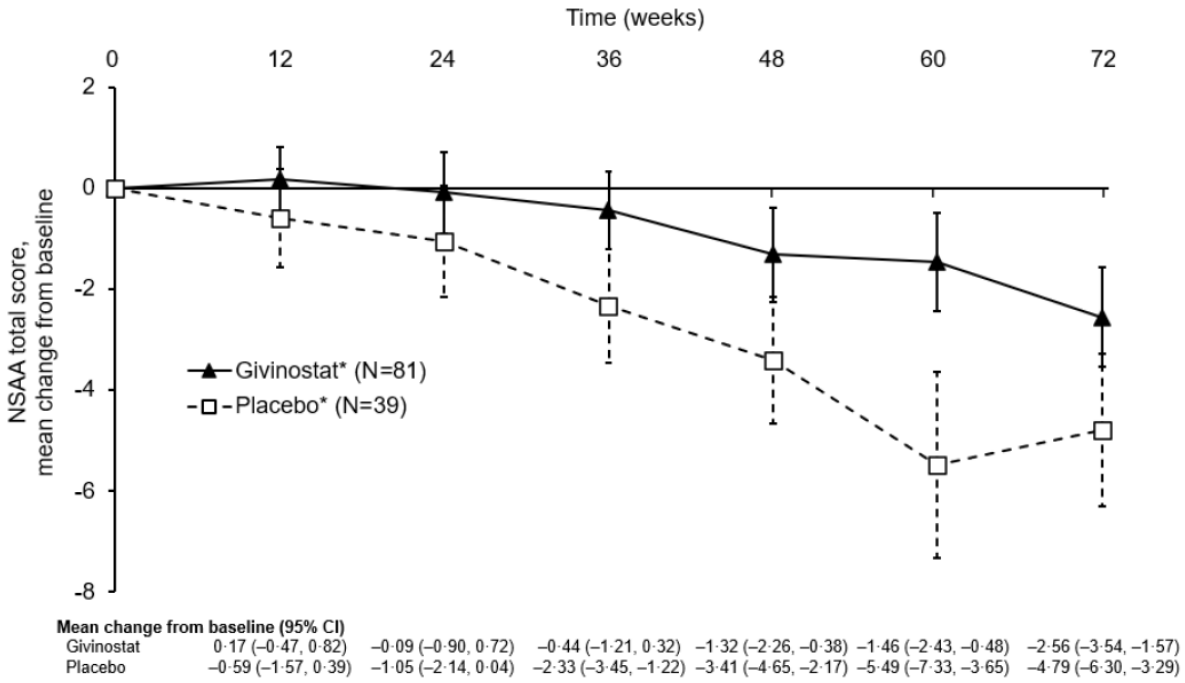

For the MRS VL MFF assessment, n=77 for givinostat and n=37 for placebo; the treatment effect estimates and CIs were standardised for presentation on the same scale, with each estimate, upper and lower CI divided by its related SE; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; 4SC results were analysed on the log scale and cumulative loss of function was analysed via negative binomial regression; direction of interpretation has been fixed accordingly
*All boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC, 4-stair climb; CI, confidence interval; ITT, intention-to-treat; MFF, muscle fat fraction; MRS, magnetic resonance spectroscopy; n, number; NSAA, North Star Ambulatory Assessment; SE, standard error; VL, vastus lateralis.
Source: Mercuri et al. 2024.[22, 132]


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### NSAA total score

NSAA is a scale assessing various aspects of functional domains associated with daily activities. The NSAA outcomes in the EPIDYS study mirrored what would be expected from the 4SC primary endpoint results. There was evidence to suggest that decrease in NSAA total score from baseline was numerically lower (i.e. less decline) with givinostat than with placebo, at 18 months (LS mean difference 1.91; 95% CI 0.30 to 3.53; p=0.021; Figure 17) and at all timepoints over the course of the study (Figure 18).[22, 132, 136]

**Figure 18: Mean change from baseline over 18 months in NSAA total score | Target ITT population**




Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 24.44 and 24.67 for the givinostat and placebo groups, respectively; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: CI, confidence interval; CS, corticosteroids; ITT, intention-to-treat; N, number; NSAA, North Star Ambulatory Assessment.
Source: Mercuri et al. 2024.[22, 132]

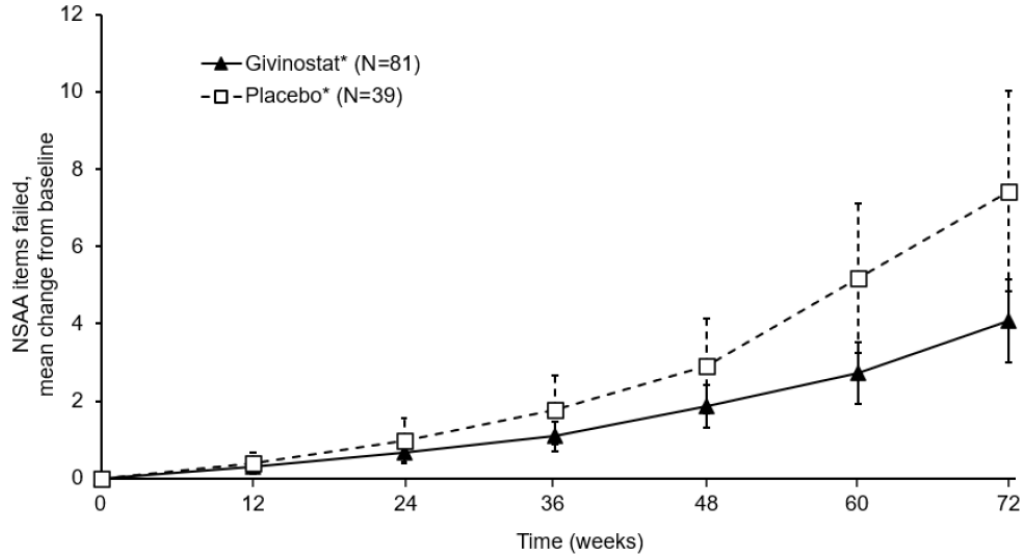
### NSAA cumulative loss of function

Cumulative loss of function was also numerically lower with givinostat than with placebo (2.14 fewer items failed over 18 months; 3.42 versus 5.56; ratio 0.61; 95% CI 0.41 to 0.93; p=0.0202; Figure 17), with fewer items failed at each timepoint (Figure 20).[22, 132, 136] This finding is important because in an analysis by the Collaborative Trajectory Analysis Project,[137] a loss of 2.0 NSAA items predicted clinically meaningful disease progression, loss of ambulation in the functionally declining group, and loss of ability to rise from the floor in the younger, more stable group. Moreover, complete loss of function in one NSAA item, or deterioration in 1 to 2 items, is perceived as an important change by boys/young men and their parents.[157] The loss of NSAA items over 18 months in the EPIDYS placebo group confirms that the boys were in a late ambulatory decline phase.


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Analysis of the effect on the 17 specific items of the NSAA showed that givinostat treatment was associated with less decline in most of the NSAA items (Figure 20), but particularly on the items that are mostly affected in boys of this age and disease stage (such as the ability to hop and jump).[144]

**Figure 19: NSAA cumulative loss of function (items failed) over 18 months | Target ITT population**

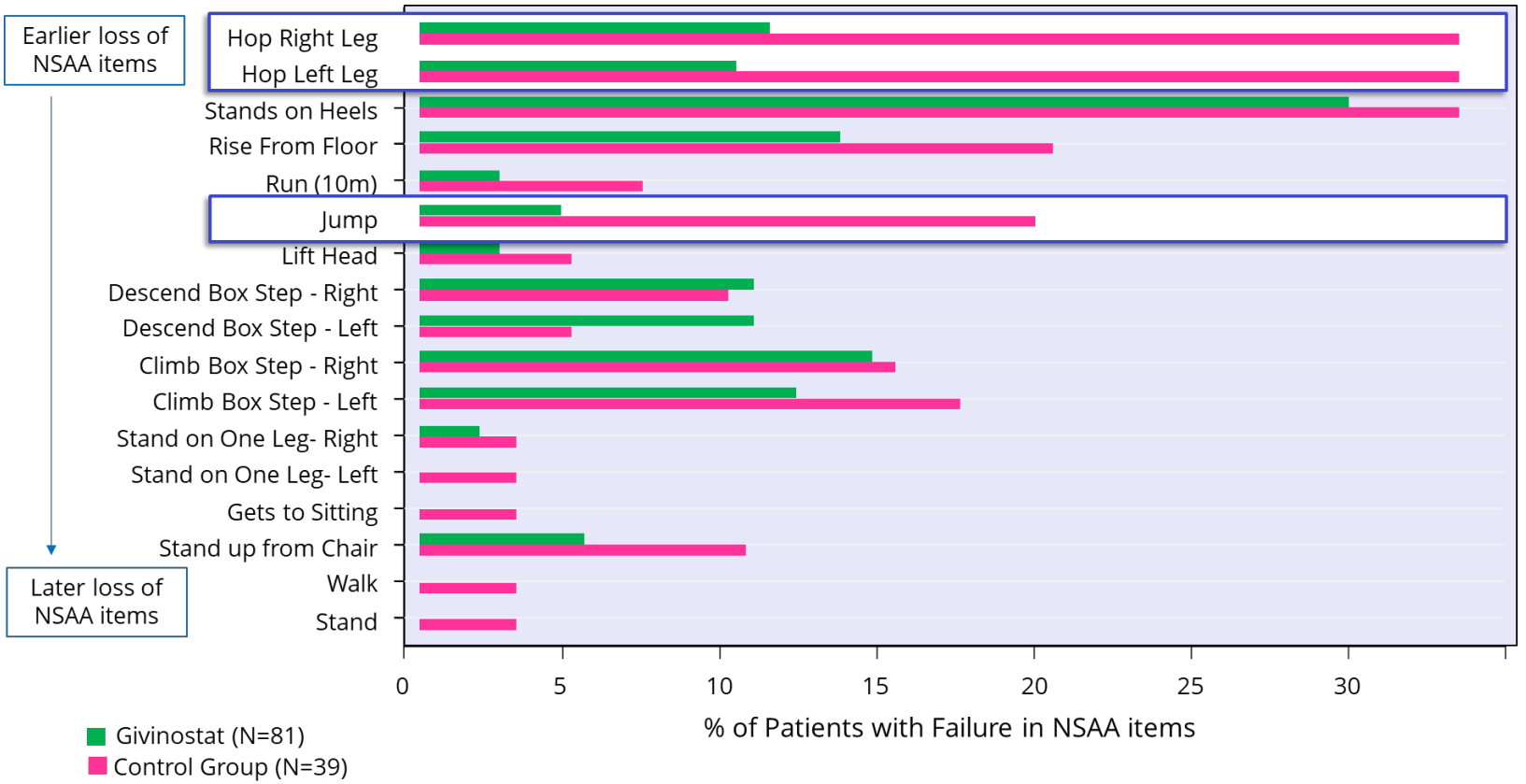



| Mean change from baseline (95% CI) | | | | | | |
|---|---|---|---|---|---|---|
| Givinostat | 0·30 (0·15, 0·44) | 0·68 (0·41, 0·95) | 1·09 (0·70, 1·47) | 1·85 (1·30, 2·41) | 2·73 (1·93, 3·53) | 4·07 (2·98, 5·16) |
| Placebo | 0·38 (0·11, 0·66) | 0·97 (0·38, 1·57) | 1·77 (0·88, 2·66) | 2·90 (1·67, 4·13) | 5·18 (3·25, 7·11) | 7·44 (4·83, 10·04) |

Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: CI, confidence interval; CS, corticosteroids; ITT, intention-to-treat; N, number; NSAA, North Star Ambulatory Assessment.
Source: Mercuri et al. 2024.[22, 132]


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**Figure 20: Loss of NSAA items at Month18 | Target ITT population**



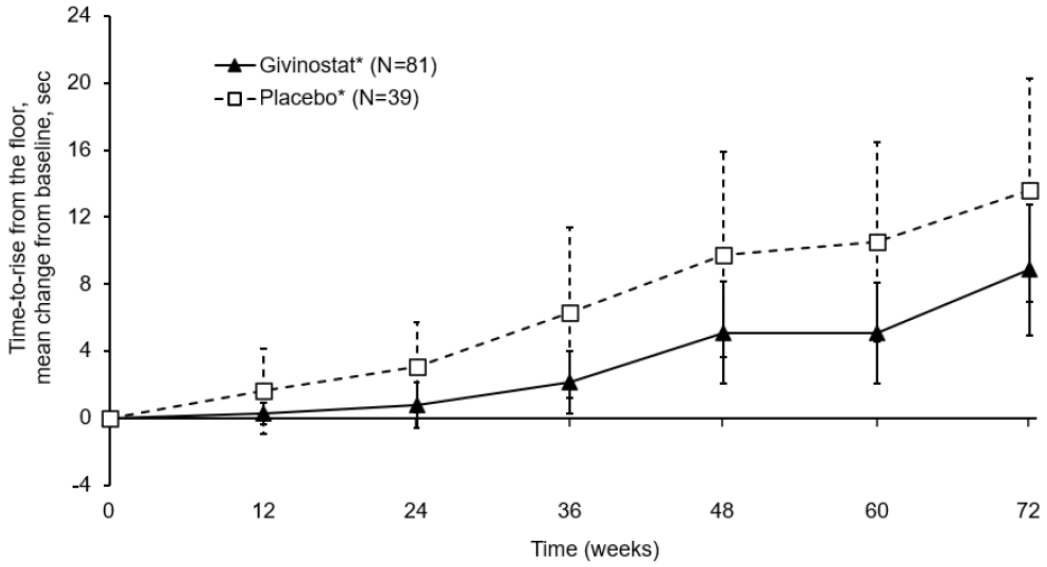

Abbreviations: ITT: intention-to-treat; n: number of boys in the study population; NSAA: North Star Ambulatory Assessment.
Source: Mercuri et al. 2023.[144]


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### Time to rise from the floor

The change from baseline in TTRF was numerically lower over 18 months with givinostat, with a LS mean difference between groups of –3.28 (95% CI –9.57 to 3.02; p=0.3044; Figure 17 and Figure 21), and with a numerically lower mean change from baseline with givinostat at all timepoints (Figure 21).[22, 132, 136] When analysed as velocity (1/time-to-rise), the LS mean difference between givinostat and placebo at 18 months was 0.03 $s^{-1}$ (95% CI 0.007 to 0.055).[22, 132] Large interpatient variability is probably the reason for the non-significant p-value; variability was lower for the analysis of velocity.[22, 132] Despite a non-statistically significant difference between the givinostat and placebo group (p=0.3044), these results show a positive trend in boys treated with givinostat and are supportive of the primary endpoint.[22, 132, 136]

**Figure 21: Mean change from baseline over 18 months in the TTRF | Target ITT population**




| Mean change from baseline (95% CI), sec | | | | | | |
|---|---|---|---|---|---|---|
| Givinostat | 0·28 (–0·38, 0·94) | 0·78 (–0·55, 2·11) | 2·14 (0·25, 4·03) | 5·08 (2·03, 8·13) | 5·08 (2·08, 8·08) | 8·86 (4·96, 12·76) |
| Placebo | 1·62 (–0·94, 4·18) | 3·06 (0·38, 5·74) | 6·30 (1·21, 11·39) | 9·76 (3·64, 15·87) | 10·51 (4·54, 16·48) | 13·59 (6·93, 20·24) |

Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 5.57 and 5.59 seconds for the givinostat and placebo groups, respectively; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: CI, confidence interval; CS, corticosteroids; ITT, intention-to-treat; N, number; TTRF, time to rise from the floor.
Source: Source: Mercuri et al. 2024.[22, 132]

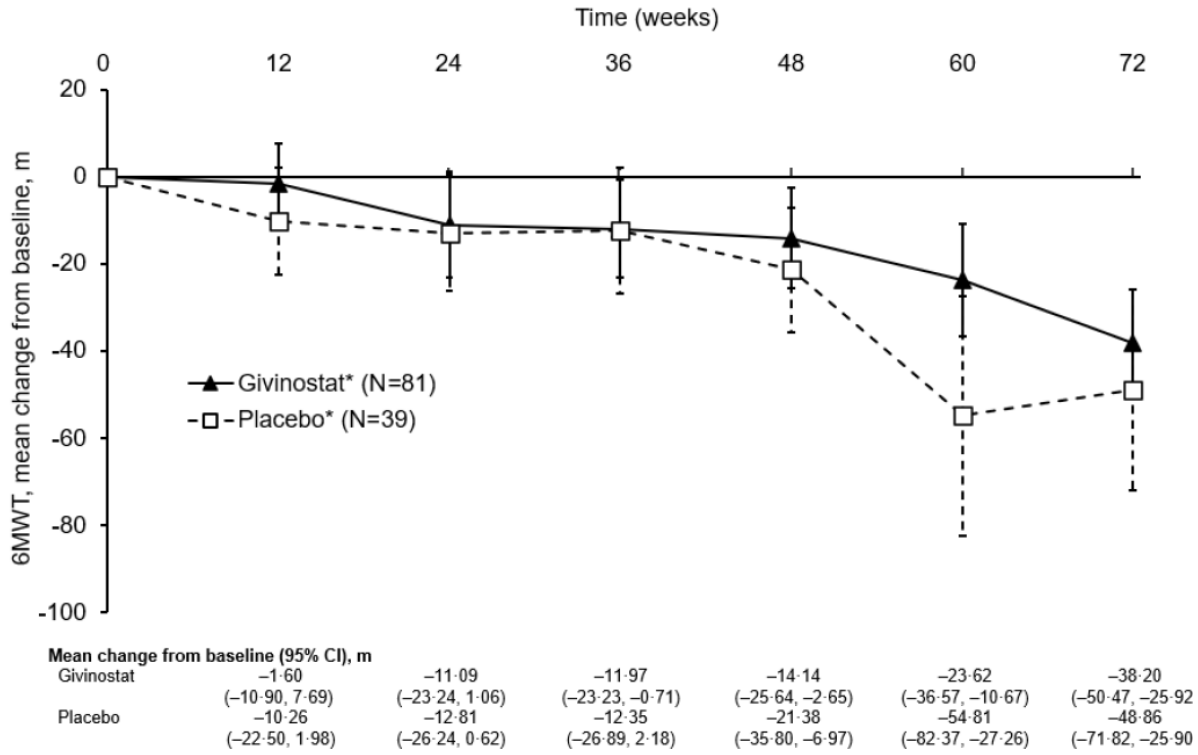
### Distance walked in 6 minutes (6MWT)

The baseline mean 6MWT was 403.3 metres for the givinostat group and 399.6 metres for the placebo group.[22, 132] The 6MWT decline over 18 months was slower with givinostat than placebo, with a LS mean difference in distance covered of 10.0 metres (95% CI –12.1 to 32.0; p=0.3723; Figure 17), with lower mean change from baseline with givinostat at all timepoints (Figure 22).[22, 132, 136] The baseline mean in each group was at least 350 metres and boys who can walk these distances are likely to have stable or only slowly declining results for this test, so demonstrating a significant treatment effect would require a much


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larger sample size.[22, 132] Despite the lack of statistically significant difference between the groups (p=0.3723), the results show a positive trend in boys treated with givinostat and are supportive of the primary endpoint. [22, 132, 136]

**Figure 22: Mean change from baseline over 18 months in the 6MWT | Target ITT population**




| Mean change from baseline (95% CI), m | | | | | | |
|---|---|---|---|---|---|---|
| Givinostat | −1·60 (−10·90, 7·69) | −11·09 (−23·24, 1·06) | −11·97 (−23·23, −0·71) | −14·14 (−25·64, −2·65) | −23·62 (−36·57, −10·67) | −38·20 (−50·47, −25·92 |
| Placebo | −10·26 (−22·50, 1·98) | −12·81 (−26·24, 0·62) | −12·35 (−26·89, 2·18) | −21·38 (−35·80, −6·97) | −54·81 (−82·37, −27·26) | −48·86 (−71·82, −25·90 |

Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 403.3 and 399.6 metres for the givinostat and placebo groups, respectively; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 6MWT, 6-minute walking test; CI, confidence interval; CS, corticosteroids; ITT, intention-to-treat; N, number
Source: Mercuri et al. 2024.[22, 132]

### Muscle strength evaluated by knee extension and elbow flexion

Changes from baseline in knee extension and elbow flexion over 18 months were numerically lower with givinostat than placebo, with LS mean differences between givinostat and placebo of 0.19 N/kg (95% CI –0.03 to 0.40; p=0.0902) for knee extension and of 0.09 N/kg (95% CI –0.04 to 0.21; p=0.1818) for elbow flexion (Figure 17 and Table 22).[22, 132, 136] The changes seen in EPIDYS were small, consistent with a study of the natural history of the disease.[173, 174]


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**Table 22: Analysis of muscle strength evaluated by knee extension and elbow flexion normalised by subject weight (N/kg), change from baseline at 18 months | Target ITT population**

| | Givinostat (N=81) | Placebo (N=39) |
|---|---|---|
| **Overall knee extension** | | |
| Number of boys included in the analysis, n (%) | 81 (100) | 39 (100) |
| LS mean | −0.32 | −0.50 |
| 95% CI for LS mean | −0.44, −0.20 | −0.68, −0.33 |
| Difference in LS means (givinostat−placebo) | 0.19 | |
| 95% CI for difference in LS means | −0.03, 0.40 | |
| P value | 0.0902 | |
| **Overall elbow flexion** | | |
| Number of boys included in the analysis, n (%) | 81 (100) | 39 (100) |
| LS mean | −0.10 | −0.19 |
| 95% CI for LS mean | −0.17, −0.03 | −0.29, −0.09 |
| Difference in LS means (givinostat−placebo) | 0.09 | |
| 95% CI for difference in LS means | −0.04, 0.21 | |
| P value | 0.1818 | |

Baseline was defined as the last non-missing value recorded prior to or on the date of first study treatment; LS means, CIs, and p-values were obtained from an analysis of covariance model on change from baseline in normalised muscle strength at Month 18 with baseline normalised muscle strength and rederived age at first dose fitted as covariates, with concomitant corticosteroid use and treatment group as independent classification factors; if more than 1 measurement was taken at a visit for a boy, the arithmetic mean of the measurements was used; the overall value was obtained by mean of the respective left and right values.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LS, least square; N, number in the analysis set; n, number of boys meeting the criterion.
Source: Mercuri et al. 2024;[22, 132] EPIDYS CSR.[136]

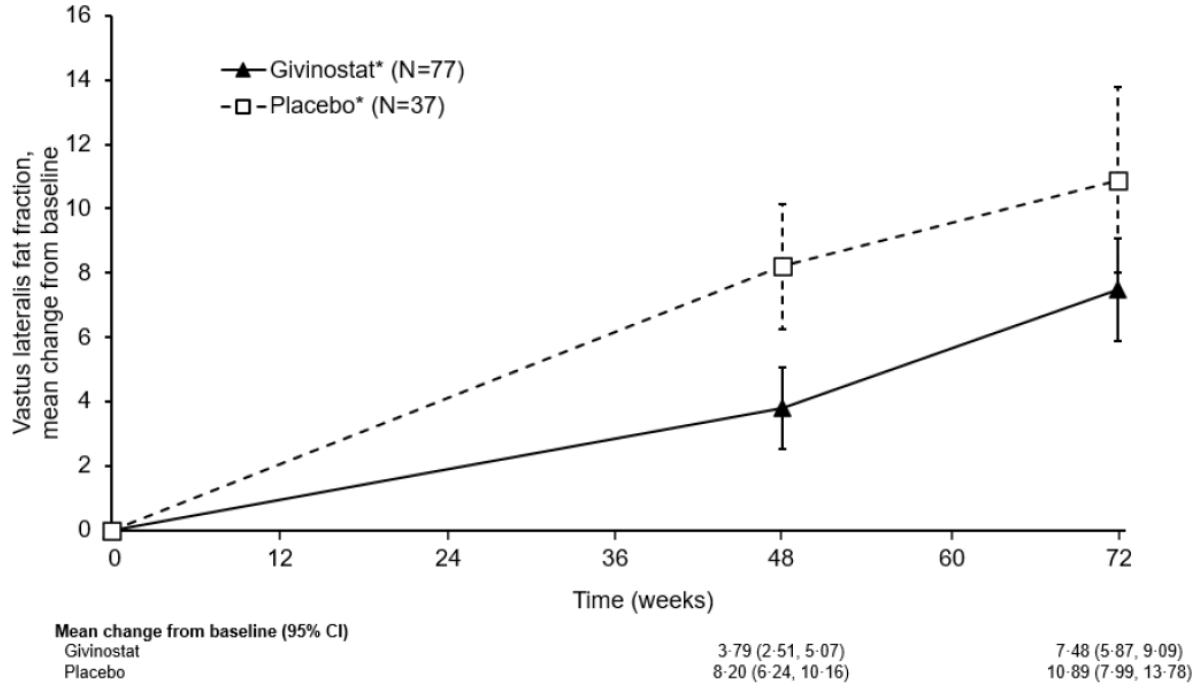
### Mean change in VL MFF

A difference between the givinostat and placebo groups was also observed using muscle imaging, a technique that provides more objective evaluations than the other outcome measures. MRS evidence suggested that there was numerically less fat infiltration in the vastus lateralis at 18 months with givinostat than with placebo (LS mean difference in fat fraction –2.92; 95% CI –5.64 to –0.20; p=0.0354; Figure 17), and the change from baseline was numerically lower in the givinostat group at all timepoints (Figure 23).[22, 132, 145] Boys in the placebo group had a baseline average VL MFF of 15.45% and an increase of 10.9%, whereas boys treated with givinostat had a baseline average of 15.95% and an increase of 7.5%.[145] The 30% reduction in VL MFF with givinostat versus placebo at 18 months is predicted to be clinically meaningful, because increased VL MFF inversely correlates with muscle function, daily activity (4SC and TTRF) and predicts loss of ambulation (baseline VL MFF value <0.2, functional ability is likely to be preserved, including ambulation, the ability to climb stairs and rise from the floor, over the subsequent 12 and 24 months; baseline VL MFF >0.3 indicates the likely loss of functional ability over the subsequent 24 months).[175–177]

Givinostat reduced fat fraction in four other thigh muscles/muscle groups important for ambulation compared with placebo at 18 months (Appendix M.5.2).[145]


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**Figure 23: Mean change from baseline over 18 months in VL MFF | Target ITT population**



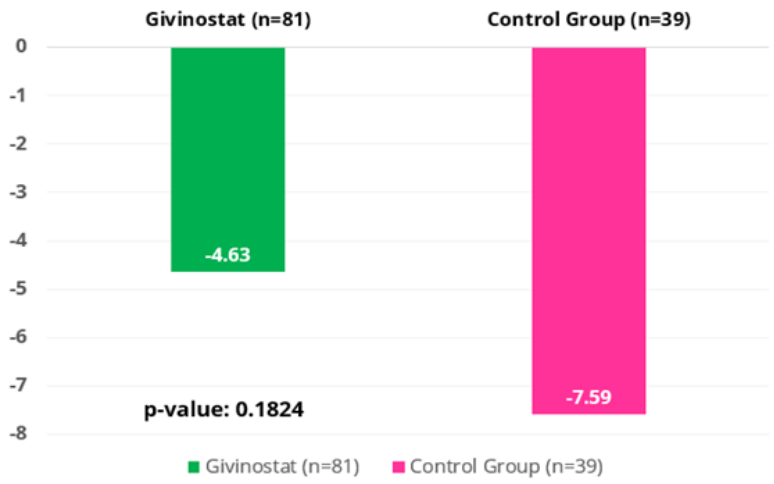

Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 15.45 and 15.95% for the givinostat and placebo groups, respectively; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: CI, confidence interval; CS, corticosteroids; ITT, intention-to-treat; N, number; VL MFF, vastus lateralis muscle fat fraction.
Source: Mercuri et al. 2024.[22, 132]

### B.2.6.3 EPIDYS | Patient-reported outcomes | Target ITT population

Givinostat treatment showed a trend towards a reduction in the decline of the HRQoL, assessed using the Pediatric Outcomes Data Collection Instrument (PODCI), for boys with DMD at 18 months when compared with the placebo group.[136] The LS mean change in the Standardised Global Function scale scores from the PODCI at 18 months was −4.63 (95% CI −7.11, −2.16) and −7.59 (95% CI −11.17, −4.01) for the givinostat and placebo groups respectively (Figure 24).[136] The difference in LS means (givinostat-placebo) of standardised global function scale scores from the PODCI was not statistically significant (LS mean difference, givinostat-placebo: 2.96; 95% CI −1.41, 7.33; p=0.1824) for change from baseline at 18 months.[136] The results from the PODCI standardised scores collected for each subscale did not show any significant difference between boys treated with givinostat versus placebo.[136] These results indicate that givinostat treatment does not negatively impact QoL, and QoL may decline less rapidly.


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**Figure 24: LS mean change from baseline in the PODCI at 18 months | Target ITT population**




Abbreviations: LS: least square; n: number of boys in the study population; ITT, intention-to-treat; n, number; PODCI: Pediatric Outcomes Data Collection Instrument.
Source: Mercuri et al. 2024.[22, 132]

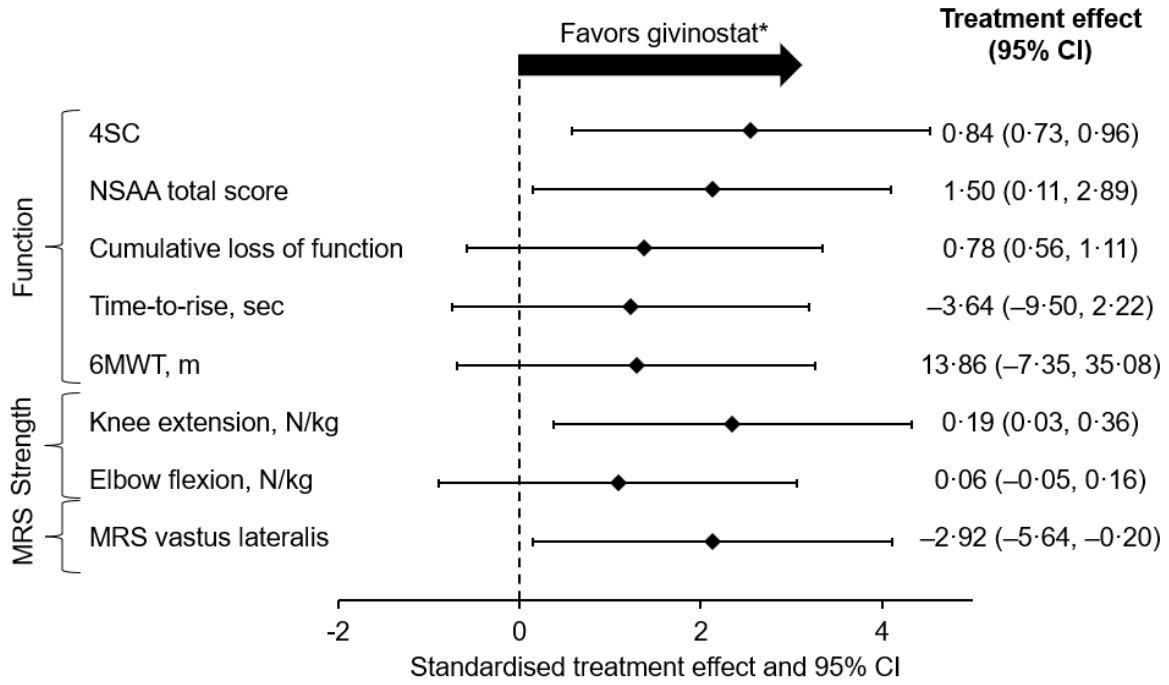
### B.2.6.4 EPIDYS | Target ITT population vs. Overall ITT population

A *post hoc* analysis of givinostat efficacy in the Overall ITT population confirmed that the results were consistent with those seen in the Target ITT population (Group A).[138] Supportive analyses were performed to evaluate the effect of givinostat compared with ECM in the Overall ITT population (N=179) (see Section B.2.4.3) on both the primary endpoint (4SC) and six key secondary endpoints (Figure 25).[138]

Over the 18-month follow-up period, 4SC decline was significantly slower with givinostat than placebo; generalised least squares (GLS) mean ratio (SD)=0.84 (0.069); p=0.0116.[138] Treatment effects relating to the key secondary endpoints consistently favoured givinostat over ECM. Givinostat treatment was associated with less decline in NSAA total score (mean difference: 1.50 points; nominal p=0.035).[138]


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**Figure 25: Forest plot of primary and key secondary endpoints at 18 months | EPIDYS Overall ITT population**




Number analysed are 118 for givinostat and 61 for placebo, except MRS vastus lateralis, which is 77 and 37, respectively; plotted treatment effect estimates and CIs were standardised to be presented on the same scale, with each estimate, upper and lower confidence interval divided by its related standard error; 4SC was analysed on the log scale and cumulative loss of function was analysed via negative binomial regression; direction of interpretation has been fixed accordingly; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walking test; CS, corticosteroids; MRS, magnetic resonance spectroscopy; NSAA, North Star Ambulatory Assessment.
Source: Mercuri et al. 2024[22, 132]; Mercuri et al. 2024b.[138]

### B.2.6.5 EPIDYS | Subgroup analysis

**Pre-planned subgroup analyses**

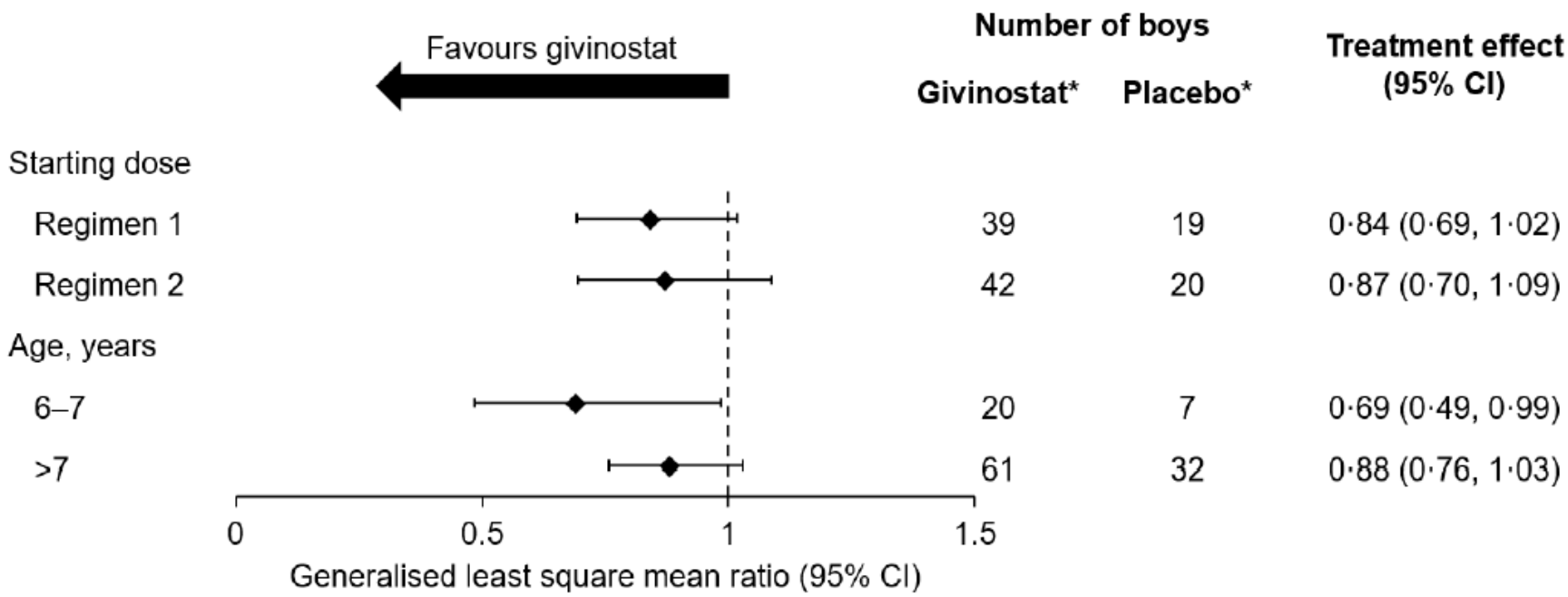
Subgroup analyses of the EPIDYS primary endpoint showed that responses across treatment groups were consistent for pre-defined subgroups defined by givinostat starting dose and age at first dose (Figure 26).[22, 132]

The median total weight-adjusted exposure (mg/kg) in the Overall ITT population was calculated to determine two subgroups: <median or ≥median. For the Target ITT population, the generalised LS mean ratio (givinostat/placebo) was 0.78 seconds for boys in the total weight-adjusted exposure ≥median subgroup for time to 4SC at 18 months for givinostat versus placebo (p=0.0206). The generalised LS mean ratio (givinostat/placebo) was 1.01 seconds for boys in the total weight-adjusted exposure <median subgroup for givinostat versus placebo (p=0.9568).[136]

All other (*post hoc)* subgroup analysis results are reported in Appendix E.


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**Figure 26: Forest plot of subgroup analyses of the primary endpoint (4SC) at 18 months | EPIDYS Target ITT population**




Givinostat Regimen 1: weight-based starting dose 20–70 mg bid, with a reduced dose of 13–47 mg bid; Regimen 2: weight-based starting dose 13–47 mg bid, with a reduced dose of 11–37 mg bid (see Supplementary Table in Appendix M.2); *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC, 4-stair climb; CI, confidence interval; CS, corticosteroids; ITT, intention-to-treat population.
Source: Mercuri et al. 2024.[22, 132]


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### B.2.6.6 OLE study | Longer-term givinostat efficacy

No formal hypothesis testing was planned for the secondary efficacy endpoints. When interpreting the efficacy and PedsQL scores results, it is important to note that there were a high number of missing values, mainly due to visits not being performed at the site due to the COVID-19 pandemic.[135] All missing values due to loss of ambulation or inability to perform the test or cases for which a clear reason for not performing the tests was not reported were imputed as Class 2 data. This led to a large amount of missing values imputed to a penalising value, meaning that the analyses are conservative.[135]

As discussed in Section B.2.3.5, the OLE study included three givinostat treatment subgroups – but as the patient numbers were small across the different outcomes and ambulatory status, we have presented pooled data for the Overall givinostat population.

**Major milestones at December 2023 DCO**

For the 195 ambulant boys at baseline:[135]

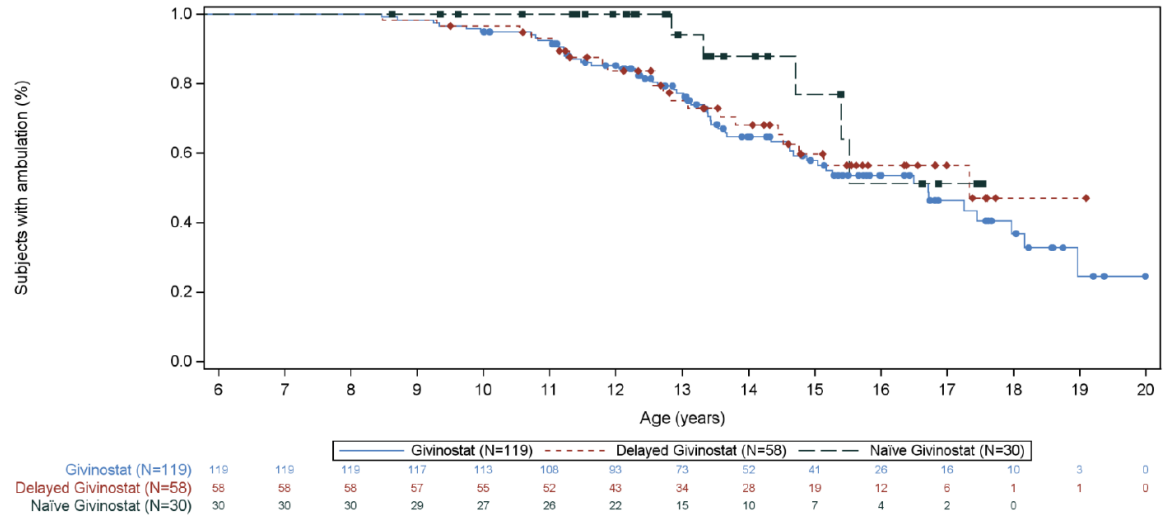
- 79 lost the ability to perform the 4SC assessment; at a median age of 16.1 years in the givinostat group and 16.5 years in the delayed givinostat group,
- 118 had at least one 10MWT >10 seconds, with a median estimated age of 13.7 to 15.5 years across the three givinostat groups
- 124 had loss of ability to rise from the floor, with a median age of 13.2 to 15.2 years across the three givinostat groups
- 145 had at least one rise from floor >10 seconds, with a median estimated age at first rise from floor of >10 seconds of 12.6 to 14.1 years across the three givinostat groups.

In the Overall ITT population (N=207; 195 ambulant and 12 non-ambulant at baseline), 78 (37.7%) young men had lost ambulation by the December 2023 DCO; the median age at loss of ambulation was 16.7 years in the givinostat group, 17.3 years in the delayed givinostat group, and not calculable in the naïve givinostat group (Figure 27).[135] This is higher than the median age expected in a DMD population treated with CS only (e.g. the estimated median age at loss of ambulation in a 2022 analysis of data from the UK North Star Network database was 11 years 8 months [interquartile range: 10 years 1 month–14 years 5 months]).[73]

By the December 2023 DCO, two young men in the givinostat group required daytime respiratory report, but the median age at first occurrence was not calculable.[135] No boys/young men required scoliosis surgery. Two boys/young men had died, but their deaths were due to incidental injury, not due to disease.[135]


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**Figure 27: KM plot of age at loss of ambulation | ITT set**




Abbreviations: ITT, intention-to-treat; KM. Kaplan-Meier.
Source: DoF (Study 51 Clinical Study Report; Dec 2023 DCO).[135]

### PUL and MFM results (Overall population)

In the Overall population (N=207), the PUL version 2.0 results showed that the distal-level (wrist and hand dimension score) was stable during the study.[135] For the mid-level (elbow dimension score), there was no decline after one year, there was a mean decline of about 1 point in the second year which was maintained in the third year, and there was a decline of about 2 points from baseline at the fourth year. For the high-level (shoulder dimension score), there was a decline of about 1 point during the first 2 years of treatment, 2 points in the third year and about 3 points from baseline in the fourth year. The mean total score was 38.5 at baseline and changed from baseline by a mean of −1.7 at Month 24, by −3,0 at Month 36 and by −5.2 at Month 48.[135]

Mean PUL version 1.2 in the first 18 boys until Month 16 was negligibly lower than baseline.[139]

Motor Functions measured with the MFM scale showed slight deterioration during the study, in the total score and in the standing and transfers domain, followed by axial and proximal motor function domain.[135] The distal motor function scores were quite stable during the study in the Overall population. In this group, the reduction in mean total score at 1 year of treatment was 2.9 points, and was 6.2, 10.6, and 14.1 points at 2, 3, and 4 years of treatment, respectively.[135]

### Secondary efficacy analyses in ambulant boys

As expected in a progressive disease, ambulant boys (n=195) showed decline during the study compared with baseline, such that in the fourth year of treatment there was a mean decrease of around 196.3 metres in 6MWT (SD 140.1 metres), 10.7 points mean decline in the NSAA total score, and more time taken for the time function tests.[135] The mean velocity of 4SC decreased by about −0.6 steps per seconds, mean velocity of walk 10 metres by


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−1.0 m/s, and rise from floor by about −0.1 1/sec.[135] The mean knee extension and elbow flexion muscle strength assessments also showed worsening over time in the Overall population.[135]

This is a slower decline that would be expected for a comparative population receiving ECM only; see Section B.2.8 where this is explored further.

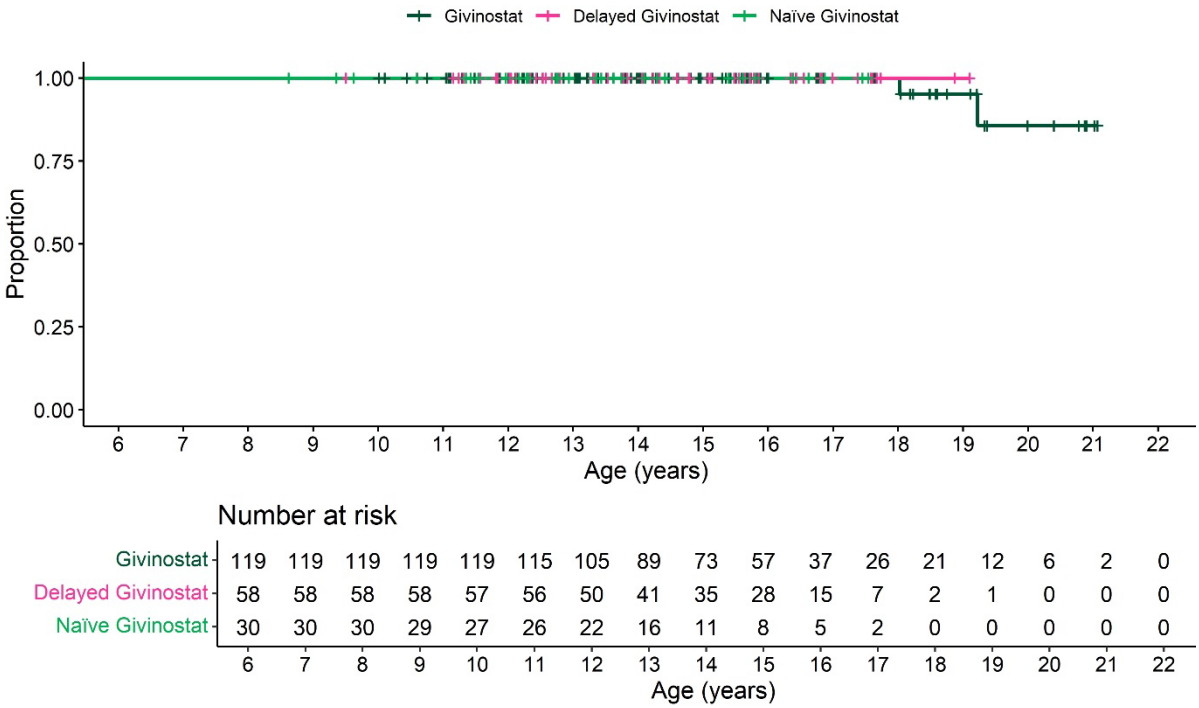
**Lung function (Overall population)**

Pulmonary function tests showed a minimal increase from baseline for FVC and forced expiratory volume in 1 second (FEV1) until 4 years of treatment; while % predicted FVC showed a steady decrease throughout the study period, with a mean fall of 3.4% in the first year of treatment, and a mean fall of about 19.7% after 4 years of treatment.[135] Peak expiratory flow (PEF) showed a steady increase throughout study and a minimal decrease of % predicted PEF with a mean value of −14.8% after 4 years of treatment.[135]

Comparison of the % predicted FVC and PEF collected in this study with published data from natural history studies, suggests no negative effects of givinostat on respiratory function, and may suggest a slowing down of disease progression.[139]

Two of the young men reached a need for daytime respiratory support (Figure 28) during follow-up; note, both patients were previously treated in Study 43.[135]

**Figure 28: KM plot of age at first occurrence of respiratory support | ITT set**




Abbreviations: ITT, intention-to-treat; KM. Kaplan-Meier.
Source: DoF (IFT analysis of date from OLE study, all patients, Dec 23 DCO).


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**HRQOL (Overall population)**

HRQoL was measured by the PedsQL, completed by parents/caregivers (the Proxy Report) and by boys/young men (the Self-Report); the study did not directly assess parent/caregiver HRQoL but patient HRQoL as perceived by parent/caregiver. A slight deterioration of HRQoL (around 5 to 10%) was seen in both child and parent PedsQL.[135]

The mean PedsQL total and dimension score for boys/young men declined from baseline over time by almost 3 points at Month 24, and by almost 5 points at Month 48; whereas mean total An dimension score assessed by parents/caregivers declined over time by around 3 points at Months 24 and 48, and by more than 4 points at Month 36.[135]

The mean PedsQL neuromuscular module total and dimension score declined from baseline over time by around 2 points at Months 12 and 24, and by almost 3 points at Months 36 and 48 (for boys/young men); whereas the decline over time was by around 3 points at Months 12 and 24, by almost 6 points at Month 36, and almost 4 points at Month 48 (for parents/ caregivers).[135]

SF-36 data were too limited at this DCO to draw any conclusions.[135]

**Additional analyses**

The results of an exploratory mixed effect random coefficient analysis suggest that givinostat effects are comparable in boys who were treated with givinostat from the first day in the clinical trial and those whose givinostat treatment was delayed by 18 months (i.e. boys who were received placebo in EPIDYS).[135, 139] The only notable difference at the Dec 2023 DCO was a difference between the two groups in the annual change for % predicted FVC (which was -4.83 and -2.85 (p=0.02) for the givinostat and delayed givinostat groups, respectively).[135]

Due to different inclusion/exclusion criteria and givinostat exposure in Study 43 and EPIDYS, an additional *post hoc* analysis was carried out excluding boys from Study 43.[139] At the Dec 2021 DCO, no significant differences between the givinostat and delayed givinostat groups were noted for all functional and pulmonary parameters. The same results were noted for all physical parameters when the analysis was done excluding the missing values.[139]

### B.2.6.7 Efficacy in young men who became non-ambulant while participating in givinostat studies

The company considers that in view of its mechanism of action, givinostat is expected to counteract muscle deterioration in all muscle types, in all phases of DMD disease, and will continue to be effective after loss of ambulation. However, givinostat has only been studied in patients who are ambulant at treatment initiation. To address question regarding extrapolation of efficacy and safety results from the current givinostat program to non-ambulant patients, the company has conducted a limited assessment of efficacy outcomes in DMD patients who have become non-ambulant while on treatment with either placebo or givinostat in Study 43, EPIDYS or the OLE.[172]

A total of 36 young men have become non-ambulant while participating in givinostat DMD clinical studies (34 patients while receiving givinostat and 2 patients while receiving placebo). The imbalance is due to the difference in the number of boys in the givinostat and


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placebo groups in the DMD Safety Set and the fact that boys who received placebo in EPIDYS and continued into the OLE were switched to receive givinostat. The small number of young men who became non-ambulant while receiving placebo precludes comparison of givinostat and placebo in this group of patients.[172]

The additional analyses on patients on givinostat who became non-ambulant show a similar trajectory in FVC% before and after loss of ambulation.[172] For FVC%, the estimated difference between the slopes pre- and post-loss of ambulation was −0.173 (95% CI: −0.451, 0.106, p=0.2163).[172]

### B.2.6.8 Conclusions | EPIDYS and OLE study

In the Phase 3 EPIDYS trial, givinostat significantly slowed the rate of disease progression and showed less decline in muscle function for boys with DMD over 18 months of treatment versus ECM. [22, 132] There was a statistically significant and clinically-meaningful slowing of decline in the ability to climb four stairs at 18 months for givinostat versus placebo (both in addition to ECM),[22, 132] translating into a 1.78 second (p=0.037) mean difference in time to climb four stairs.[22, 132] Subgroup analyses were consistent with the primary endpoint data.[22, 132] These changes in muscle function would likely lead to improved participation in physical and social activities of daily life, and are predictive of a delay in loss of ambulatory ability.

Secondary endpoint data show that givinostat is likely to provide benefits compared with placebo on other daily living activities important to boys with DMD (such as running, jumping hopping, and rising from a chair).[22, 132] The mean difference versus placebo in change from baseline in NSAA total score was 1.91 (nominal p=0.021).[22, 132] Similar results were obtained for cumulative loss of function on the NSAA (nominal p=0.0202).[22, 132] The mean difference versus placebo in change from baseline in TTRF was 3.28 seconds (nominal p=0.3044), and the mean difference versus placebo in change from baseline in distance walked (metres) at the end of the 6MWT was 10.0 metres (nominal p=0.3723).[22, 132]

Consistent with the benefits seen on daily activities, muscle strength evaluated by knee extension or elbow flexion showed numerically less decline with givinostat than placebo at 18 months.[22, 132] Treatment with givinostat also reduced fat infiltration in VL muscle by approximately 30% (LS mean difference for givinostat-placebo: –2.92%; nominal p=0.035). As well as providing further evidence of delayed DMD progression, lower VL MFF correlates with daily activity and predicts loss of ambulation.[22, 132]

Together these changes in muscle function endpoints indicate a slowing of disease progression, and the potential for a delay in loss of ambulation. Indeed, givinostat showed a slower progression of important endpoints compared with what would be expected in patients receiving ECM; see the results of ITCs presented in Section B.2.8.

The mean change in Standardised Global Function scale scores from PODCI, as well as subscale scores, showed a trend towards a reduction in the decline of the HRQoL for givinostat versus placebo but did not reach statistical significance at 18 months (p=0.1824).[136]

Longer-term efficacy data from the OLE study support the continued benefit of givinostat treatment. At the fifth interim analysis of the ongoing OLE study, descriptive analyses indicate a slower deterioration of muscle function than would be expected in ambulant boys


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receiving ECM, but also suggest a delay in the occurrence of major disease milestones, including loss of ambulation.[135] The median age of the loss of ambulation in the givinostat group was 16.7 years,[135] considerably higher than the median age expected in a DMD population treated with CS only (11 years 8 months in a 2022 analysis of data from the UK North Star Network database).[73]


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## B.2.7 Meta-analysis

Not applicable.

## B.2.8 Indirect and mixed treatment comparisons

The EPIDYS trial provides key milestone data for delay in disease progression for patients receiving givinostat in addition to ECM, compared with ECM without givinostat, across an 18-month follow-up. Over the follow-up period of the study, givinostat demonstrated meaningful benefits versus ECM. The OLE study continues to collect long-term data specifically for givinostat. In the absence of comparative data for long-term outcomes, the relative efficacy of givinostat in addition to ECM compared with ECM is derived using ITCs. These data are used to inform the transitions between health states in the CEM.

The givinostat evidence base is formed by two clinical studies[22, 132, 133, 134, 139] and the ECM evidence base is UK real-world data[40]. As the UK real-world data and the givinostat evidence do not have a common comparator, unanchored matching-adjusted indirect comparisons (MAICs) are utilised to derive the relative efficacy of givinostat versus ECM. The MAICs aim to evaluate the relative effects of givinostat on ambulatory and non-ambulatory function, by comparing age at disease milestones (e.g. age at loss of ambulation) between givinostat and ECM.

### B.2.8.1 Summary of studies included in the indirect treatment comparison

**Evidence base**

Two primary evidence sources inform the ITC analyses for givinostat, EPIDYS (described in Section B.2.3.1) and the OLE study (Study 51; described in Section B.2.3.5). Patients in the two givinostat studies were eligible to be included in the ITC if they had received givinostat from study entry, i.e. patients who were randomised to placebo in EPIDYS and who received delayed givinostat in the OLE study were excluded given the treatment effect in those patients will be confounded. Patients enrolled in EPIDYS who went on to enrol in the OLE study were assessed based on their most recent follow-up to avoid double counting. Patients who were enrolled in Study 51 but were previously enrolled in Study 43 were excluded due to different inclusion/exclusion criteria and givinostat exposure in Study 43 and EPIDYS.

A published UK real-world data source is the most appropriate data source to use to estimate the efficacy of patients receiving ECM, as this reflects both the UK DMD population and UK clinical practice[40, 178]. A sensitivity analysis compares givinostat with ECM using international data from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS), excluding patients who were naïve to corticosteroid treatment or had received investigational drugs for DMD in previous clinical trials.[179, 180] The published CINRG data used in the sensitivity analysis are comparable to that presented in NICE highly specialised technology (HST) appraisal 22 to form an ITC versus ataluren; however, given this study is not as recent as the UK real-world data and it was not conducted in UK centres, it was not considered for the base case ITC analyses.[7, 180, 181] The results of the sensitivity analyses are presented in Appendix D, Section D.2.8.1.


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The UK real-world data reflects a multicentre, retrospective case note review study including 209 patients who were treated at University College London, the Newcastle upon Tyne or Oxford university hospitals. Patients were stratified into three groups: CS naïve (taken CS for 12 months or less; n=53); CS stopped (used CS for at least 12 months but stopped prior to transition to adult services; n=43); and CS continued (continued CS into adulthood; n=113).

Table 23 summarises the study design of EPIDYS, the OLE study and the UK real-world data. In total, 148 patients receiving givinostat were included in the ITC: 102 patients were enrolled in both EPIDYS and the OLE study; 16 patients were enrolled in EPIDYS only and 30 patients were receiving givinostat for the first time in the OLE study. For patients receiving ECM, 156 patients were included in the ITC, 113 of whom received continuous CS, and 43 patients had stopped CS treatment prior to transitioning to adult services. Patients who received CS for <12 months were not included in the analysis as this group are not reflective of UK clinical practice.


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**Table 23: Study design of the studies included in the indirect treatment comparison**

| Study | Treatment intervention | N | Phase/ blinding | Centre | Study design | Sample size for ITC |
|---|---|---|---|---|---|---|
| EPIDYS (Study 48) (NCT02851797) | Givinostat | 118 | Phase 3, double-blind | Multicentre | RCT | 118 pts:<br>• 102 pts were also enrolled in OLE study<br>• 16 pts unique to EPIDYS |
| | Placebo | 61 | | | | NA |
| OLE study (Study 51)† (NCT03373968) | Givinostat | 110 | Long-term study, open-label | Multicentre | Enrolling patients who have been previously treated in previous givinostat studies or who met all inclusion/ exclusion criteria for EPIDYS, but had baseline MRS VLFF in range ≤5% or >30% | 132 pts:<br>• 102 pts previously treated with givinostat in EPIDYS<br>• 30 pts who were givinostat naïve at study start‡ |
| | Delayed givinostat | 54 | | | | |
| | Naïve givinostat‡ | 30 | | | | |
| UK real-world data | CS stopped prior to transition to adult services | 43 | NA | London, Newcastle and Oxford | Retrospective case note review | 156 pts receiving ECM |
| | CS continued to adulthood | 113 | | | | |
| | CS naïve | 53 | | | | NA |

†Dec 2023 DCO; ‡Met all the inclusion criteria and none of the exclusion criteria for EPIDYS, and not randomised as enrolment in the "off-target" group was completed, subjects received givinostat for the first time in the OLE study.
Abbreviations: CS, corticosteroid; DCO, data cut off; ECM, established clinical management; ITC, indirect treatment comparison; MRS VLFF, magnetic resonance spectroscopy vastus lateralis fat fraction; NA, not applicable, NR, not reported; OLE, open-label extension; pts, patients; UK, United Kingdom.


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**Baseline characteristics**

Baseline characteristics for each of the patient groups included in the ITC by study and pooled are reported in Table 24. There was minimal availability of baseline characteristics in the UK real-world data; only CS start age was reported. The UK real-world data patients (pooled CS stopped and CS continued) started CS at an older age (7.20 years) compared with pooled EPIDYS and the OLE study (6.09 years). Due to the real-world evidence nature of the data set, it is unknown how comparable other characteristics were across the datasets. However, the UK real-world data represent a clinically relevant population who would be eligible to receive givinostat in the UK.

**Table 24: Baseline characteristics of studies included in the indirect treatment comparison**

| | EPIDYS | OLE study | Pooled EPIDYS/ OLE study | UK real-world data | | Pooled ECM UK real-world data |
|---|---|---|---|---|---|---|
| **Treatment** | Givinostat | Givinostat | Givinostat | CS stopped | CS continued | Combined CS (=ECM) |
| **N** | 118 | 30 | 148 | 43 | 113 | 156 |
| **Age (years)** | | | | | | |
| **Mean (SD)** | 9.78 (2.02) | 10.5 (2.25) | 9.92 | NR | NR | NR |
| **Range** | 6.30 to 15.9 | 6.10 to 14.4 | 6.10 to 15.9 | NR | NR | NR |
| **CS start age (years)** | | | | | | |
| **Mean (SD)** | 6.11 (1.74) | 6.03 (2.37) | 6.09 (1.88) | 7.19 (1.73) | 7.20 (1.96) | 7.20 (1.90) |
| **Range** | 3.12 to 12.6 | 1.38 to 10.9 | 1.38 to 12.6 | 4 to 11.5 | 4 to 12.42 | 4 to 12.42 |
| **Race, n (%)** | | | | | | |
| **White** | 106 (89.8) | 22 (73.3) | 128 (86.5) | NR | NR | NR |
| **Asian** | 4 (3.4) | 2 (6.7) | 6 (4.1) | NR | NR | NR |
| **Black/ African American** | 3 (2.5) | 1 (3.3) | 4 (2.7) | NR | NR | NR |
| **Other** | 5 (4.2) | 5 (16.7) | 10 (6.8) | NR | NR | NR |
| **BMI (kg/m$^2$)** | | | | | | |
| **Mean (SD)** | 19.7 (4.10) | 20.2 (4.04) | 19.8 (4.08) | NR | NR | NR |
| **Range** | 12.4 to 30.6 | 13.9 to 30.5 | 12.4 to 30.6 | NR | NR | NR |
| **Time since first CS initiation (years)** | | | | | | |
| **Mean (SD)** | 3.62 (2.09) | 4.47 (2.65) | 3.80 (2.23) | NR | NR | NR |
| **Range** | 0.43 to 8.88 | 0.91 to 12.6 | 0.43 to 12.6 | NR | NR | NR |
| **Use of CS at baseline, n (%)** | | | | | | |
| **Deflazacort** | 91 (77.1) | 27 (90.0) | 118 (79.7) | NR | NR | NR |
| **Other steroid** | 27 (22.9) | 3 (10.0) | 30 (20.3) | NR | NR | NR |
| **Time to rise from floor (sec)** | | | | | | |
| **Mean (SD)** | 6.89 (7.43) | 5.57 (2.06) | 6.62 (6.71) | NR | NR | NR |
| **Range** | 2.60 to 60.2 | 3.00 to 9.50 | 2.60 to 60.2 | NR | NR | NR |
| **Time to 4SC (sec)** | | | | | | |


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| | EPIDYS | OLE study | Pooled EPIDYS/ OLE study | UK real-world data | | Pooled ECM UK real-world data |
|---|---|---|---|---|---|---|
| **Mean (SD)** | 3.58 (1.25) | 3.58 (1.28) | 3.58 (1.25) | NR | NR | NR |
| **Range** | 1.80 to 7.10 | 1.80 to 6.60 | 1.80 to 7.10 | NR | NR | NR |
| **Time to walk/run 10 metres** | | | | | | |
| **Mean (SD)** | 5.56 (1.34) | 19.0 (74.6) | 8.28 (33.6) | NR | NR | NR |
| **Range** | 3.50 to 9.50 | 3.20 to 414 | 3.20 to 414 | NR | NR | NR |

Abbreviations: 4SC, 4-stair climb; BMI, body mass index; CS, corticosteroids; ECM, established clinical management; NR, not reported; OLE, open-label extension; SD, standard deviation; sec, second.

### Outcome availability

Table 25 shows the outcome measure availability for the studies included in the ITC. The UK real-world data reported both Kaplan-Meier (KM) curves and medians for age at non-invasive ventilation (NIV), time to predicted forced vital capacity (pFVC) <30%[a], age at forced vital capacity (FVC) <1L and overall survival (OS). In addition, medians were reported for age at loss of ambulation, age at pFVC <60%, age at pFVC <50% and age at pFVC <60%. The EPIDYS and the OLE studies collected the same endpoints as the UK real-world data, as well as additional endpoints including age at loss of 4SC and age at loss of rise from floor; however, for age at NIV, subsequent non-ambulatory health states and overall survival the data are immature with no events observed. Therefore, alternative methods were required to estimate the KM curves for these outcomes at later follow-ups to enable an ITC to be conducted (described in Section B.2.8.2). Additionally, where the UK real-world data only reports a median, alternative methods were required to estimate the KM to allow a more robust ITC to be conducted (also described in Section B.2.8.2).

**Table 25: Outcome availability for the studies included in the indirect treatment comparison**

| Outcome | Pooled EPIDYS/OLE study | | UK real-world data | | |
|---|---|---|---|---|---|
| | Givinostat group | | ECM group | | |
| | Reported | Note | Reported | Median reported | KM reported |
| **Age at LOA** | Y | - | Y | Y | N |
| **Age at loss of 4SC** | Y | - | N | N | N |
| **Age at loss of rise from floor** | Y | - | N | N | N |
| **Age at NIV** | Y | No events available for analysis† | Y | Y | Y |
| **Age at pFVC <50%** | Y | | Y | Y | N |
| **Age at pFVC <30%** | Y | | Y | Y | N |
| **Age at FVC <1L** | Y | | Y | Y | Y |

[a] Note this was not reported as *age at* time to pFVC <30%


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| Outcome | Pooled EPIDYS/OLE study | | UK real-world data | | |
|---|---|---|---|---|---|
| | Givinostat group | | ECM group | | |
| | Reported | Note | Reported | Median reported | KM reported |
| **Additional outcomes available, but not of interest for ITC and CEM** | | | | | |
| **Age at pFVC <60%** | Y | No events available for analysis† | Y | Y | N |
| **Time to pFVC <30%** | Y | | Y | Y | Y |
| **OS** | Y | | Y | Y | Y |

†Zero events were reported for age at first occurrence of respiratory support in the OLE study (see Figure 28).
Abbreviations: 1L, 1 litre; 4SC, 4-stair climb; ECM, established clinical management; FVC, forced vital capacity; IPD, individual patient data; ITC, indirect treatment comparison; KM, Kaplan-Meier; LOA, loss of ambulation; NIV, non-invasive ventilation; pFVC, predicted forced vital capacity.

### B.2.8.2 Overview of the methodology

**Matching-adjusted indirect comparison (MAIC) overview**

From the included studies, individual patient data (IPD) were available for patients receiving givinostat whilst aggregate-level data were available for those receiving ECM. One methodology that can be used to derive the relative efficacy of givinostat versus ECM when IPD for all trials are not available, are MAICs. The MAICs are unanchored as there is no common comparator to link givinostat with ECM beyond the initial follow-up period of 18 months reported for the EPIDYS trial. The MAIC methods used are in line with the published guidance in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18, and Phillippo 2018.[182, 183]

The MAIC approach adjusted for baseline differences in potential prognostic factors and treatment effect modifiers by re-weighting the available IPD for givinostat to match the average baseline characteristics of the ECM treatment group, for which only aggregate data are reported. MAIC is a non-parametric likelihood reweighting method that allows a propensity score logistic regression model to be estimated with the potential prognostic factors and treatment effect modifiers as predictors in the model. Re-weighting the IPD through MAIC methods in this way can reduce (or remove) observed imbalances in patient characteristics between two treatments. Outcomes for each treatment can then be compared between the balanced trial populations. To account for the fact that weights are estimated rather than fixed and known, standard errors (SE) for the MAIC estimates were calculated using both a robust sandwich variance estimator and a bootstrap estimator as per recommendations in the NICE DSU TSD 18 guidance.[182] Further details of the MAIC methodology are presented in Appendix D, Section D.2.5 and D.2.7.

Age at start of CS therapy was available from the UK real-world data and this was included as a matching variable in the MAIC. Where there was a published KM curve for a specific outcome, the proportion event-free was extracted using Engauge Digitizer 12.1, and pseudo-IPD was reconstructed using the algorithm published by Guyot 2012.[184]


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**Acceleration factor overview**

As presented in Table 25, a limitation with the data available is the lack of reported KM data for loss of ambulation for the UK real-world data and the immature data available for non-ambulatory outcomes for givinostat. Therefore, acceleration factors were utilised to enable comparison from the available data, in addition to make a population-adjustment via the MAIC.

***Loss of ambulation***

Although it is possible to conduct time-to-event ITCs using median survival estimates to calculate a hazard ratio (HR) for the comparison between two treatments,[185] this approach assumes that the hazard of experiencing an event is constant over time. This assumption is clearly violated if outcomes are modelled from birth and patients do not experience loss of ambulation until a few years after birth. Additionally, for loss of ambulation, the median is only reached for the givinostat dataset at the end of the KM curve where there are very few patients still at risk (median survival for givinostat was not reached post-weighting in the MAIC, making the HR from medians not estimable). Given these limitations, it was not deemed appropriate to directly compare the medians between the treatment arms.

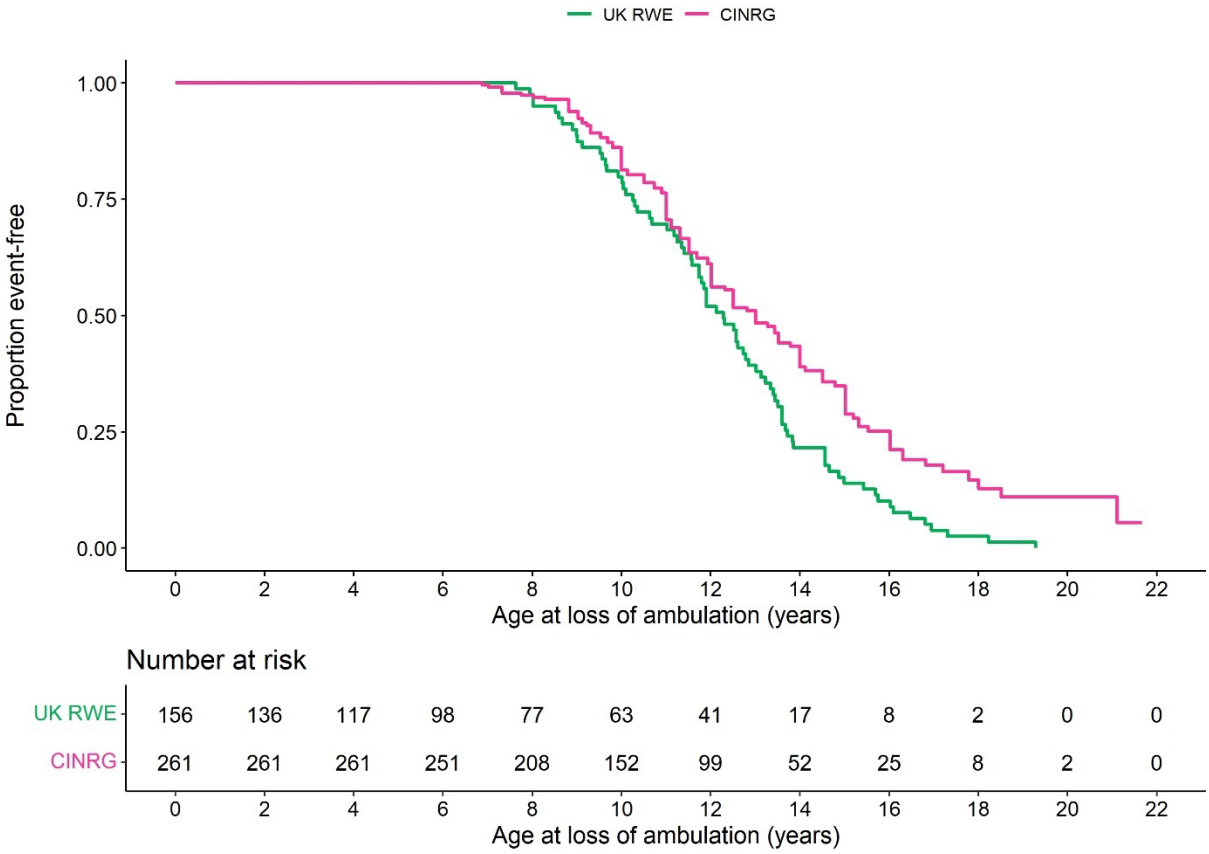
Therefore, an alternative approach was considered to generate a KM curve for age at loss of ambulation for ECM, which involved the following steps using the published UK real-world data:

- The KM curves for the age at NIV were digitised for both the CS stopped and continued groups
- Acceleration factors were derived between age at loss of ambulation and age at NIV, by dividing the median age at loss of ambulation and median age at NIV for the CS stopped and continued groups
- The derived acceleration factors were applied to the digitised age at NIV KM data to provide estimated age at loss of ambulation. By applying an acceleration factor the analysis assumes that the shape of the KM curve between the outcomes is the same but loss of ambulation events occur at a multiple of time earlier. Note, given that loss of ambulation is expected to occur prior to a patient receiving NIV, it was considered conservative not to re-censor patients.

Utilising this approach generates a KM curve which is a broadly similar shape to the CINRG DNHS loss of ambulation KM curve (see Figure 29) although patients in the UK real-world data are typically estimated to experience loss of ambulation at a slightly younger age which is in line with the reported median age at loss of ambulation in the two studies (UK real-world data [CS stopped; n = 43]: 10.67 years [10.31, 11.55]; UK real-world data [CS continued; n = 113]: 12.67 [12.37, 13.45]; CINRG [n=261]: 13.0 [12.0, 14.0]).


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**Figure 29: Comparison of acceleration factor estimated UK real-world data loss of ambulation Kaplan-Meier curve with the observed CINRG DNHS loss of ambulation Kaplan-Meier curve**




Abbreviations: CINRG DNHS; Cooperative International Neuromuscular Research Group Duchenne Natural History Study; KM, Kaplan-Meier; UK, United Kingdom.

***Non ambulatory patients***

As the lung function outcomes for givinostat are immature, with zero events occurring during the study follow-up period for respiratory support (Figure 30), it is not possible to form a direct comparison with ECM nor to extrapolate the givinostat KM data for these outcomes. Consequently, an alternative approach was used to estimate the KM data for the non-ambulatory outcomes for givinostat.

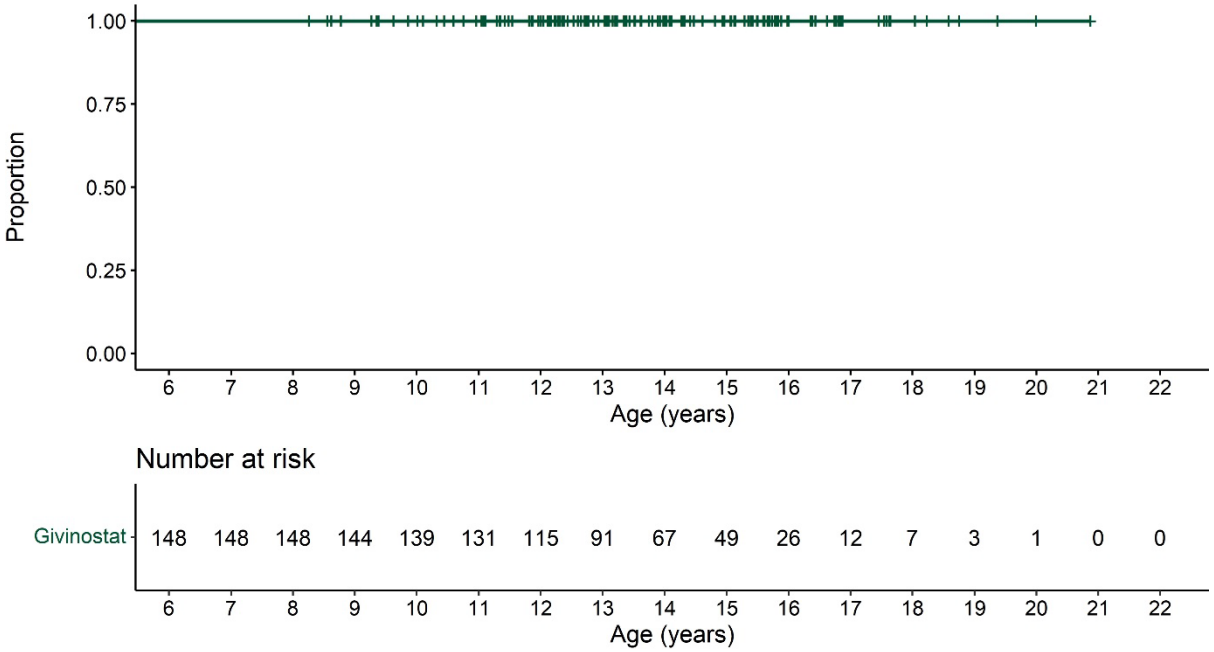
- Using both the estimated median age at loss of ambulation and the median age at each available respiratory outcome from the UK real-world data, an acceleration factor was derived between age at loss of ambulation and age at the respiratory outcome
- The acceleration factor was then applied to the givinostat age at loss of ambulation data to provide an estimated age for each of the non-ambulatory outcomes.

This approach assumes that the relationship between the age at loss of ambulation and the age respiratory outcomes is the same for both givinostat and ECM. Humbertclaude et al. 2012 found that age at loss of ambulation is predictive of both the age at which the peak FVC is realised, and the absolute peak obtained FVC.[186] These findings are supported by McDonald et al. 2018b who demonstrate age at loss of ambulation predicts time to an absolute FVC of 1 L and Levine et al. 2023 who show that the decline in percentile predicted


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FVC and total lung capacity correlate with age and loss of ambulation.[187, 188] Therefore, it is expected that the improved skeletal muscle integrity/ function achieved through treatment with givinostat compared to ECM, as demonstrated through the earlier outcomes observed in EPIDYS and the OLE study, will translate to improved longer term outcomes – regardless of whether a patient remains on treatment with givinostat.

**Figure 30: KM plot of age at first occurrence of respiratory support | givinostat (EPIDYS and OLE study)**




Abbreviations: ITT, intention-to-treat; KM. Kaplan-Meier.
Source: DoF (IFT analysis of date from OLE study, all patients, Dec 23 DCO).

### B.2.8.3 ITC analyses conducted

The MAIC analyses conducted are presented in Table 26.

**Table 26: Matching adjusted indirect treatment comparisons conducted**

| Endpoint | Givinostat data | ECM data | AFT estimate | Matching variables |
|---|---|---|---|---|
| Age at LOA | Age at LOA KM | Age at NIV KM for CS stopped / CS continued applying AFT of 0.67 / 0.66, respectively | AFT estimated from median age at LOA for ECM / median age at NIV for ECM:<br>CS stopped = 10.67/16 = **0.67**<br>CS continued = 12.67/19.17 = **0.66** | CS start age (years) |
| Age at NIV | Age at LOA KM with AFT of 1.50 | Age at NIV KM | AFT estimated from median age at NIV for ECM / median age at LOA for ECM: 18.46/12.28† = **1.50** | CS start age (years) |
| Age at FVC <1L | Age at LOA KM with AFT of 1.94 | Age at FVC <1L KM | AFT estimated from median age at FVC <1L for ECM / median age at LOA for ECM: 23.86/12.28† = **1.94** | CS start age (years) |

†Estimates for ECM from combined CS stopped and continued groups.
Abbreviations: 1L, one litre; AFT, acceleration factor; CS, corticosteroids; ECM, established clinical management; FVC, forced vital capacity; KM, Kaplan-Meier; LOA, loss of ambulation; NIV, non-invasive ventilation.


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### B.2.8.4 Results

Table 27 presents the givinostat studies (unadjusted and weighted) and baseline characteristics for ECM for the conducted analyses in the base case. Matching was based on age at start of CS treatment. The effective sample size (ESS) was 105.1, a reduction of around one-third smaller than the original sample size of 148 givinostat patients, suggesting reasonable overlap in patient characteristics for age at start of CS treatment.

**Table 27: Comparison of baseline characteristics: givinostat (EPIDYS and OLE Study) vs. ECM (UK real-world data)**

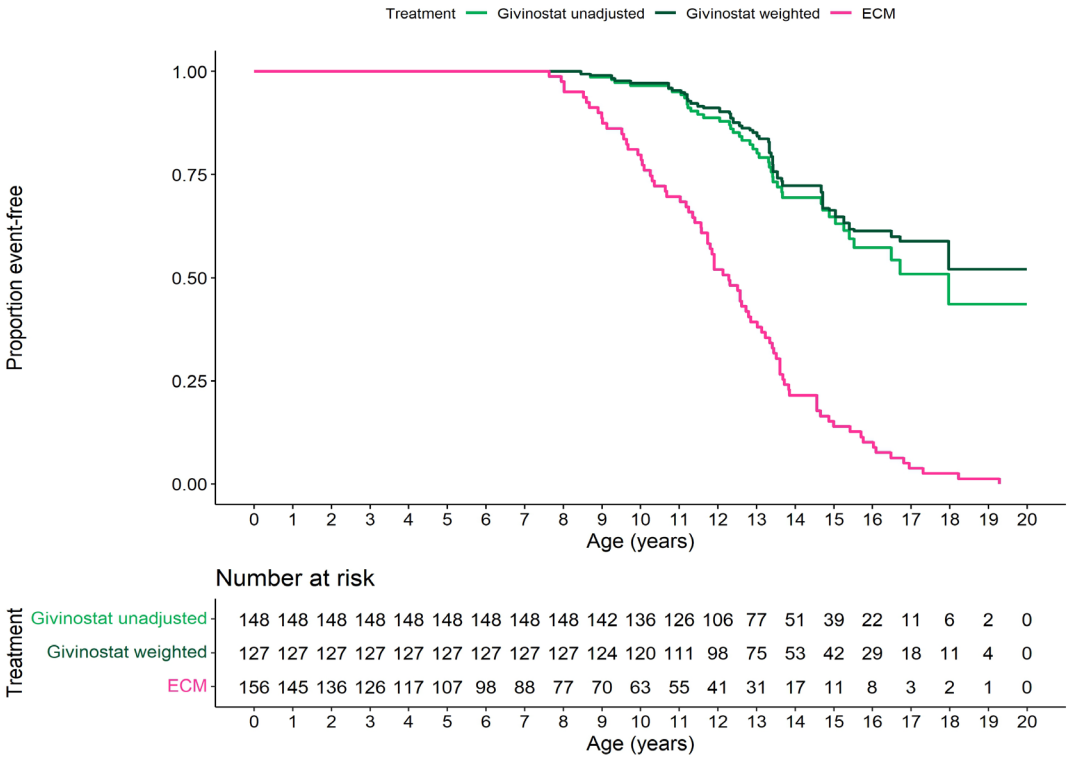
| Treatment arm | N/ESS | CS start age (years) |
|---|---|---|
| Givinostat unadjusted | 148.0 | 6.09 |
| Givinostat weighted | 105.1 | 7.20 |
| ECM | 156.0 | 7.20 |

Abbreviations: CS, corticosteroids; ECM, established clinical management; ESS, effective sample size.

#### Age at loss of ambulation

The KM plots for age at loss of ambulation for givinostat patients for both unadjusted and weighted patient data, compared with patients receiving ECM (estimated using an acceleration factor) are presented in Figure 31.

**Figure 31: Kaplan-Meier plot for age at LOA MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**




Abbreviations: ECM, established clinical management; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; OLE, open-label extension; UK, United Kingdom.


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Median age at loss of ambulation for givinostat treated patients was 18.0 years pre-weighting and not reached post-weighting, compared with 12.3 years for ECM treated patients (Table 28). This estimate of age at loss of ambulation for patients receiving ECM was consistent with evidence from CINRG,[180, 187] and considered the most relevant estimate for the UK. Patients treated with givinostat were significantly older at loss of ambulation compared with patients treated with ECM, with HR (95% CI) of 0.19 (0.12, 0.28) from the weighted comparison with robust SE; these results were aligned with results from the bootstrap estimation (HR [95% CI] 0.18 [0.12, 0.26]; Table 28). Findings from an assessment of the validity of the proportional hazards assumption are presented in Appendix D, Section D.2.8.3.


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**Table 28: Summary of age at LOA MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**

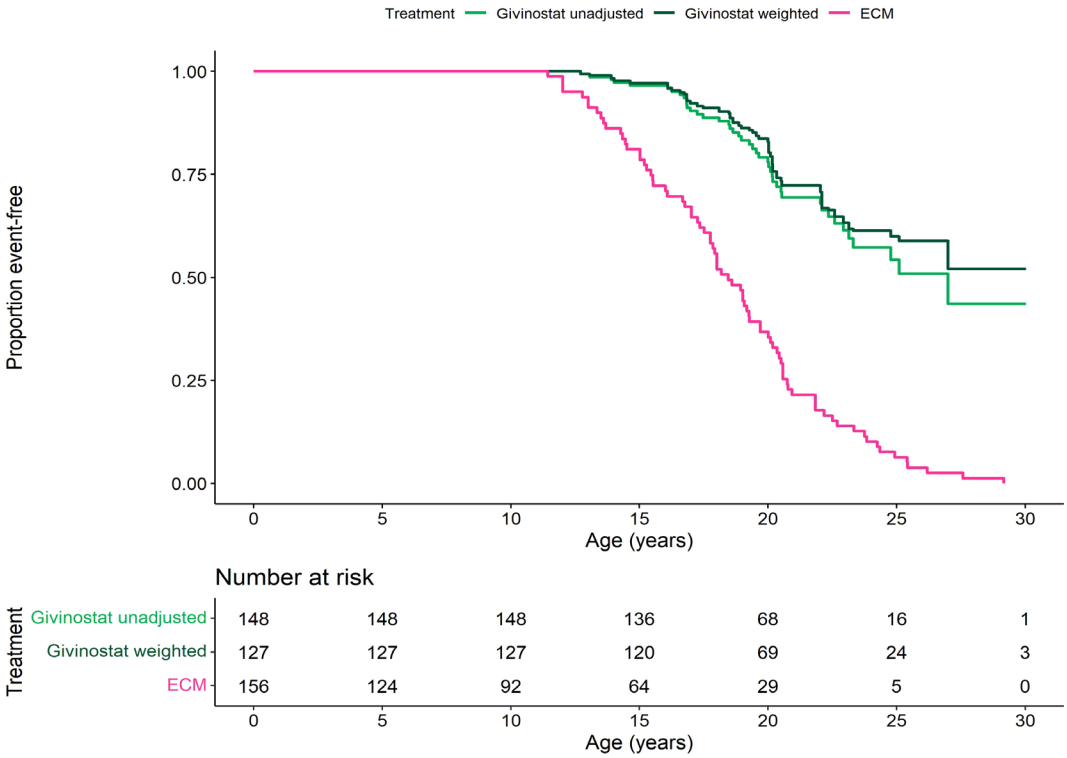
| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 17.97 (15.40, NE) | **0. 222 (0.153, 0.323)** |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NE (15.52, NE) | Robust SE: **0.185 (0.121, 0.282)** Bootstrap: **0.184 (0.127, 0.261)** |
| ECM (UK real-world data) | 156.0 | 79 | 12.28 (11.74, 13.13) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.

### Age at non-invasive ventilation

As noted previously, there were zero events for age at NIV amongst the patients receiving givinostat during the study follow-up (see Figure 28). However, applying the estimated acceleration factor to the age at loss of ambulation data (Table 26), KM curves for estimated age at NIV for givinostat patients for the unadjusted and weighted patient data, compared with patients receiving ECM are presented in Figure 32.

**Figure 32: Kaplan-Meier plot for age at NIV MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**




Abbreviations: ECM, established clinical management; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; UK, United Kingdom.


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Median age at NIV for givinostat treated patients was 27.0 years pre-weighting and not reached post-weighting, compared with 18.5 years for ECM treated patients (Table 29). Patients treated with givinostat were significantly older when receiving NIV, compared with patients treated with ECM with a HR (95% CI) of 0.19 (0.12, 0.29) from the weighted comparison with robust SE; these results were aligned with the results of the bootstrap estimation (HR [95% CI] 0.19 [0.13, 0.26];Table 29). Findings from an assessment of the validity of the proportional hazards assumption are presented in Appendix D, Section D.2.8.3.

**Table 29: Summary of age at NIV MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. EBM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 27.00 (27.14 to NA) | **0.228 (0.157, 0.332)** |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NA (23.32 to NA) | Robust SE: **0.190 (0.124, 0.290)** Bootstrap: **0.191 (0.130, 0.264)** |
| ECM (UK real-world data) | 156.0 | 79 | 18.46 (17.76 to 19.70) | Comparator |

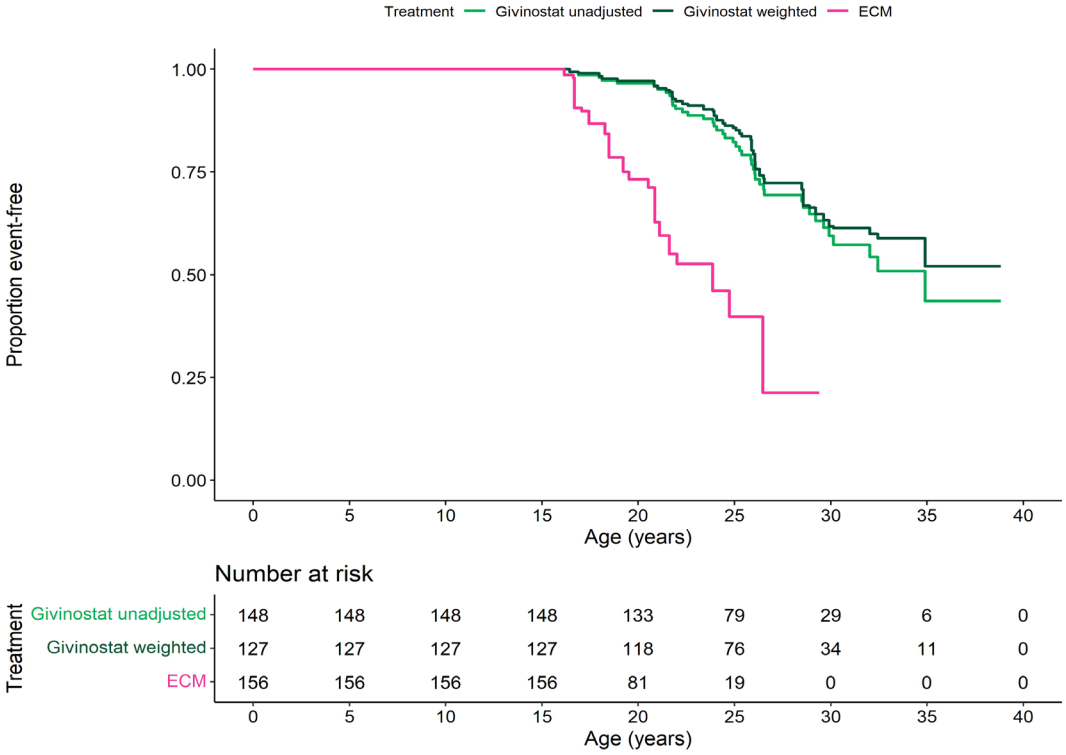
**Bold text** indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; EBM, established clinical management; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; NIV, non-invasive ventilation; OLE, open-label extension; SE, standard error.

### Age at forced vital capacity <1L

As with age at NIV, there were zero events for FVC <1L amongst the patients receiving givinostat during the EPIDYS study follow-up. However, applying the estimated acceleration factor to the age at LOA data (Table 26), KM curves for estimated age at FVC <1L for givinostat patients for the unadjusted and weighted patient data, compared with patients receiving ECM are presented in Figure 33.


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**Figure 33: Kaplan-Meier plot for age at FVC <1L MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**




Abbreviations: 1L, 1 litre; FVC, forced vital capacity; MAIC, matching-adjusted indirect comparison.

Median age at FVC <1L for givinostat treated patients was 34.9 years pre-weighting and not reached post-weighting, compared with 23.9 years for ECM treated patients (Table 30). Patients treated with givinostat were significantly older when reaching FVC <1L compared with patients treated with ECM with a HR (95% CI) of 0.21 (0.14, 0.33) from the weighted comparison with robust SE; these results were aligned with the results of the bootstrap estimation (HR [95% CI] 0.21 [0.15, 0.29]; Table 22). Findings from an assessment of the validity of the proportional hazards assumption are presented in Appendix D, Section D.2.8.3.

**Table 30: Summary of age at FVC <1L MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 34.90 (29.91, NA) | **0.233 (0.154, 0.353)** |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NA (30.14, NA) | Robust SE: **0.214 (0.139, 0.329)** Bootstrap: **0.214 (0.151, 0.288)** |
| ECM (UK real-world data) | 156.0 | 67 | 23.86 (21.62, 26.47) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: 1L, 1 litre; CI, confidence interval; ECM, established clinical management; ESS, effective sample size; FVC, forced vital capacity; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.


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### B.2.8.5 Uncertainties in the indirect and mixed treatment comparison

The uncertainties associated with this ITC are primarily due to the immaturity of the givinostat outcome data for non-ambulatory events (no events were observed for respiratory support) and the data availability for the UK real-world data.

Given the immaturity of the givinostat non-ambulatory outcome data, the relationship between outcomes within the UK real-world data has been utilised to derive pseudo-outcome data for both treatments using acceleration factors based on median survival. The use of the acceleration factor is supported for ECM given that within the CINRG DNHS the accelerated failure time assumption appears to hold between outcomes (see Appendix D.2.8.4) and the estimated acceleration factors for each outcome appear consistent between the UK real-world data and CINRG DNHS (see Appendix D; Appendix Table 15). Within the conducted ITC analysis it is assumed that the acceleration factor relationship between loss of ambulation and lung function outcomes is applicable to patients treated with givinostat, and that the observed delays in loss of ambulation correspond to delays in lung function outcomes.

The limited availability of loss of ambulation KM data and baseline characteristic information for the patients included in the UK real-world data are both limitations of the analysis. Although the ECM data source is the most relevant data source for the decision problem, the exact inclusion criteria are unknown, and CS start age is the only baseline characteristic reported. As such, it is unknown whether patients in the evidence base had systematic differences in disease characteristics and whether patients in the study may have received experimental treatment that could have improved their outcome (including givinostat). The lack of reported baseline characteristics is also an important limitation for the statistical analyses as unanchored MAICs rely on the assumption that all prognostic factors and treatment effect modifiers are controlled for.[183] This analysis only controls for differences in CS start age; however, there are a number of other factors which may impact the prognosis of DMD patients (an overview of potential prognostic factors is presented in Appendix D, Section D.2.4). The sensitivity analysis comparing with CINRG DNHS data (presented in Appendix D.2.8.3) allowed for additional characteristics to be matched on and these indirect comparisons displayed consistent results to the UK real-world data comparison, in terms of the direction and statistical significance of the estimated treatment effects, which were in favour of givinostat.

Overall, the ITCs allow for a comparison between patients treated with givinostat using trial data with a population of patients receiving ECM using a UK population which displays outcomes in line with other published data sources, including evidence from the CINRG DNHS. The results of the ITC analyses suggest that DMD patients treated with givinostat are likely to experience a significant delay in both ambulatory and non-ambulatory function.


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## *B.2.9 Adverse reactions*

### B.2.9.1 EPIDYS

The Safety population was used for safety evaluations and comprised all randomly assigned boys who received at least one dose of study drug (i.e. the Overall ITT population), with treatment group assignment defined by the treatment received.[22, 132]

The EPIDYS primary publication and CSR use different, interchangeable adverse event (AE) terminology. Following an overview of treatment compliance, givinostat exposure, dose modifications and treatment discontinuation, we present data relating to the following terms:

- Adverse events (AEs): in EPIDYS, boys received givinostat or placebo, both in addition to ECM, including CS. The AE outcomes seen during the study therefore occurred on a background of CS treatment.
- Serious adverse events (SAEs)
- Treatment-related AEs, which are specific to givinostat (as discussed below, these are known known to be associated with givinostat treatment and are generally manageable with dose modification).

**Treatment compliance and exposure**

Treatment compliance was high, and 95% of boys completed the study.[22, 132] The mean treatment duration was 493 days and was similar in all groups (givinostat, placebo, Target ITT population, and Group B).[22, 132] Mean compliance was greater than 98% in all groups (98.3% for givinostat and 98.1% for placebo overall; 98.7% for givinostat and 98.0% for placebo in the Target ITT population).[22, 132] Dosing was changed to Regimen 2 after 82 (46%) boys had been randomly assigned, but a *post hoc* ANCOVA analysis suggests that this was unlikely to have affected the results (Section B.2.6.1).[22, 132] One boy, who was receiving placebo, lost ambulation at Week 60.[22, 132]

**Dose modifications and treatment discontinuation**

Boys received a flexible-dose regimen in EPIDYS, aimed at maximising efficacy, starting with a high dose that was reduced if treatment was not tolerated.[22, 132] In DMD, patients are continually being reviewed and dose modifications for treatments such as CS are common (see Section B.1.3.7 and Figure 9).[11]

In the Overall ITT population (Groups A and B), 72.9% of boys in the givinostat group and 45.9% of boys in the placebo group had dose modifications; these were due to AEs in 45.8% and 8.2% boys, respectively.[136] Givinostat dose modifications included dose increases (6/118; 5.1%), dose reductions (57/118; 48.3%), doses permanently stopped (10/118; 8.5%), doses temporarily stopped (19/118; 16.1%), and doses skipped (47/118; 39.8%), though as detailed in Section B.2.6.1, this did not lead to a loss of efficacy.[136] Of the dose reductions in EPIDYS, 95% were driven by a laboratory finding of reversible thrombocytopaenia or hypertriglyceridaemia (the two remaining cases were due to moderate abdominal pain and moderate diarrhoea).[136]


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Givinostat showed a statistically significant positive effect on 4SC despite the dose modifications seen in the study (see results of the *post hoc* ANCOVA analysis in Section B.2.6.1).[22, 132] The flexible-dose regimen was successful in that 95% of boys completed the EPIDYS study, there were very few severe AEs, and only 3% boys receiving givinostat discontinued treatment due to AEs (all due to increased blood triglyceride).[22, 132]

**AEs**

A summary of AEs at 18 months for the Overall ITT EPIDYS population (Groups A and B) is provided in Table 31. Similar proportions of boys had AEs in both groups (112 [95%] of 118 boys receiving givinostat versus 57 [93%] of 61 boys receiving placebo, demonstrating that many of the AEs reported were due to the concomitant therapies, such as CS, that boys were receiving, rather than being related to givinostat; Table 31).[22, 132] There was no considerable difference in the incidence of AEs based on the total weight-adjusted exposure or based on the starting dose of givinostat.[136] Most AEs in both treatment groups were mild to moderate in severity (91% in the givinostat group and 92% in the placebo group).[22, 132, 136]

The most common AEs in the givinostat group (not necessarily related to the treatment) were diarrhoea, decreased platelet count or thrombocytopaenia, vomiting nasopharyngitis, headache, increased triglycerides and abdominal pain (Table 32).[22, 132] The only severe AE in two or more boys was vomiting.[22, 132]

Comparison of short-term safety data (within 3 months of treatment initiation) vs. long-term data (after 3 months of treatment) show that AEs occur more frequently in the first 3 months of treatment.[140] Diarrhoea and vomiting were less frequent in the long-term than the short-term (15.3% vs. 29.7% and 14.4% vs. 21.2% respectively). Likewise, abdominal pain was 8.5% in long-term versus 16.1% in the short-term, and episodes of low platelet count and thrombocytopaenia were less frequent after 3 months of treatment than in the first 3 months of treatment initiation (5.1% vs.14.4% and 6.8% vs.10.2% respectively).[140]


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**Table 31: Summary of AEs | EPIDYS Safety population**

| System organ class<br>Preferred term | Givinostat* (N=118)<br>Boys (%) | Placebo* (N=61)<br>Boys (%) |
|---|---|---|
| **Total number of AEs** | 112 (95%) | 57 (93%) |
| **Total number of serious AEs** | 8 (7%) | 2 (3%) |
| **Total number of boys with AEs leading to withdrawal** | 3 (3%) | 0 |
| **Fatal AEs** | 0 | 0 |
| **Total number of boys with AEs leading to permanent discontinuation of the study drug** | 4 (3%) | 0 |
| **Total number of boys with AEs leading to temporary discontinuation of the study drug** | 16 (14%) | 4 (7%) |
| **Total number of boys with AEs leading to dose reduction** | 42 (36%) | 1 (2%) |
| **Severity[1]** | | |
| Mild (Grade 1) | 69 (59%) | 39 (64%) |
| Moderate (Grade 2) | 38 (32%) | 17 (28%) |
| Severe[2] (Grade 3) | 5 (4%) | 1 (2%) |
| Life-threatening[3] (Grade 4) | 0 | 0 |
| Death related to AE (Grade 5) | 0 | 0 |

[1]If a boy experienced more than one AE, the boy was counted once at the most severe or most related event; [2]included severe or medically significant but not immediately life-threatening AEs; [3]included severe or life-threatening AEs; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: AE, adverse event; CS, corticosteroids; n, number of boys in the study population;.
Source: Mercuri et al. 2024;[22, 132] EPIDYS CSR.[136]

**Table 32: Most common AEs | EPIDYS Safety population**

| AEs | Givinostat* (N=118) | Placebo* (N=61) |
|---|---|---|
| Diarrhoea | 43 (36%) | 11 (18%) |
| Decreased platelet count or thrombocytopenia | 38 (32%) | 0 |
| Vomiting | 34 (29%) | 8 (13%) |
| Nasopharyngitis | 31 (26%) | 19 (31%) |
| Headache | 28 (24%) | 14 (23%) |
| Increased blood triglyceride concentration or hypertriglyceridaemia | 27 (23%) | 4 (7%) |
| Abdominal pain | 25 (21%) | 9 (15%) |
| Upper abdominal pain | 17 (14%) | 7 (11%) |
| Fall | 15 (13%) | 13 (21%) |


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| | | |
|---|---|---|
| Pyrexia | 15 (13%) | 5 (8%) |
| Cough | 13 (11%) | 9 (15%) |
| Pain in extremity | 8 (7%) | 7 (11%) |
| Upper respiratory tract infection | 7 (6%) | 8 (13%) |
| Back pain | 6 (5%) | 8 (13%) |
| Rhinitis | 6 (5%) | 7 (11%) |

Data are number of boys (%); events are listed by % of boys; data are grouped by treatment received at baseline; table shows MedDRA preferred terms that occurred in ≥10% boys in either group for AEs or AEs leading to dose reduction; ≥5% boys in either group for treatment-related AEs; and ≥2 boys in either group for AEs leading to treatment interruption or withdrawal, serious, and severe AEs; the thresholds were selected for clarity of reporting and to highlight the most commonly reported MedDRA preferred terms only; the severity of the AEs was assessed and graded by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (June 14, 2010); *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: AE, adverse events; CS, corticosteroids; MedDRA, Medical Dictionary for Regulatory Activities; N, number of boys in the study population.
Source: Mercuri et al. 2024.[22, 132]

### Deaths and SAEs

No boys died during the study.[22, 132]

Overall, eight (7%) boys in the givinostat group and two (3%) boys in the placebo group reported at least one serious adverse event (SAE) (Table 33).[22, 132] No SAEs were considered related to the study drug or led to withdrawal.[22, 132] SAEs in the givinostat group included gastroenteritis, gastroenteritis viral, influenza, abdominal pain, vomiting, chest pain, spinal fracture, dizziness, and rash - all reported by one (1%) boy each.[22, 132]

**Table 33: Summary of SAEs by MedDRA system organ class and preferred set | EPIDYS Safety population**

| | Givinostat* (N=118) | | Placebo* (N=61) | |
|---|---|---|---|---|
| | Event | N (%) | Event | N (%) |
| Total number of SAEs | 9 | 8 (6.8) | 2 | 2 (3.3) |
| Infections and infestations | 3 | 3 (2.5) | 2 | 2 (3.3) |
| Gastroenteritis | 1 | 1 (0.8) | 2 | 2 (3.3) |
| Gastroenteritis viral | 1 | 1 (0.8) | 0 | 0 |
| Influenza | 1 | 1 (0.8) | 0 | 0 |
| Gastrointestinal disorders | 2 | 2 (1.7) | 0 | 0 |
| Abdominal pain | 1 | 1 (0.8) | 0 | 0 |
| Vomiting | 1 | 1 (0.8) | 0 | 0 |
| General disorders and administration site conditions | 1 | 1 (0.8) | 0 | 0 |
| Chest pain | 1 | 1 (0.8) | 0 | 0 |
| Injury, poisoning, and procedural complications | 1 | 1 (0.8) | 0 | 0 |
| Spinal fracture | 1 | 1 (0.8) | 0 | 0 |
| Nervous system disorders | 1 | 1 (0.8) | 0 | 0 |
| Dizziness | 1 | 1 (0.8) | 0 | 0 |
| Skin and subcutaneous tissue disorders | 1 | 1 (0.8) | 0 | 0 |
| Rash | 1 | 1 (0.8) | 0 | 0 |


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If a boy experienced more than one AE, the boy was counted once for each SOC and once for each PT; SOCs were ordered in decreasing frequency of the total number of boys with AEs reported in each SOC, and PTs were ordered within a SOC in decreasing frequency of the total number of boys with each AE; AEs were coded using MedDRA version 24.1.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of boys in the analysis set; PT, preferred term; SAE, serious AE; SOC, system organ class.
Source: EPIDYS Clinical study report (2022).[136]

### Treatment-related AEs

Treatment-related AEs (and AEs leading to dose reduction) were more common with givinostat than with placebo (Table 34), although these were typically known to be associated with givinostat treatment (e.g. diarrhoea, thrombocytopaenia, and hypertriglyceridaemia).[22, 132] In the givinostat group, 81/118 boys (69%) had an AE that was considered to be treatment-related, versus 17/61 boys (28%) in the placebo group.[22, 132]

None of the severe or serious AEs were treatment-related or resulted in study withdrawal.[22, 132]

**Table 34: Treatment-related AEs | EPIDYS Safety population**

| Treatment-related AEs | Givinostat* (N=118) | Placebo* (N=61) |
|---|---|---|
| Treatment-related AEs | 81 (69%) | 17 (28%) |
| Decreased platelet count or thrombocytopaenia | 37 (31%) | 0 |
| Increased blood triglyceride concentration or hypertriglyceridaemia | 26 (22%) | 4 (7%) |
| Diarrhoea | 25 (21%) | 2 (3%) |
| Abdominal pain | 16 (14%) | 2 (3%) |
| Upper abdominal pain | 9 (8%) | 1 (2%) |
| Vomiting | 7 (6%) | 0 |

Data are number of boys (%); events are listed by % of boys; data are grouped by treatment received at baseline; table shows MedDRA preferred terms that occurred in ≥5% boys in either group for treatment-related AEs; *all boys were also receiving systemic CS, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: AE, adverse events; CS, corticosteroids; MedDRA, Medical Dictionary for Regulatory Activities; N, number of boys in the study population.
Source: Mercuri et al. 2024.[22, 132]

### Selected safety events of clinical interest

Diarrhoea, decreased platelet count, and hypertriglyceridaemia are recognised AEs of givinostat and can generally be managed by dose reduction or interruption (as was the case in EPIDYS as 95% of boys completed the study, and treatment compliance was high).[22, 132] Platelet reduction is a known AE associated with HDAC inhibitors, including givinostat, and is considered to be related to their pharmacological effect.[18]


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***Diarrhoea***

Diarrhoea was more common in the givinostat group, occurring in 43 (36%) boys versus 11 (18%) in the placebo group.[22, 132] This was considered to be treatment-related in 21% of the givinostat group.[22, 132] One boy in the givinostat group withdrew from the study due to diarrhoea. [136]

***Decreased platelets***

A reduction in mean platelet count between baseline and 18 months was observed in boys receiving givinostat but not in those receiving placebo, although platelet counts were highly variable.[22, 132] In the givinostat group, 67 (57%) of 118 boys had a shift from normal to low platelet counts during the study (compared with three [5%] of 61 in the placebo group); in 33 (28%) of these 118, the dose of givinostat was reduced due to decreased platelet count (23 [42%] of 55 on Regimen 1 and ten [16%] of 63 on Regimen 2).[22, 132] The thrombocytopaenia events leading to dose reduction were mild and reversible; no events resulted in study withdrawal and none was associated with clinical signs such as excessive bleeding.[22, 132, 136]

***Increased triglyceride levels***

Mean triglyceride concentrations increased from baseline to 18 months; 70 (59%) of 118 boys receiving givinostat had a shift from normal to high triglyceride concentrations during this time, compared with 30 (49%) of 61 boys receiving placebo.[22, 132] The AEs of increased blood triglyceride concentrations or hypertriglyceridaemia were more common with givinostat (27 [23%] of 118 boys) than with placebo (four [7%] of 61 boys); two such events, each in a boy receiving givinostat, resulted in study withdrawal, but were not severe or serious AEs.[22, 132] Events of hypertriglyceridaemia leading to dose reduction (n=10) were mild in two cases and moderate in the remaining eight, with the highest value being <3× the upper limit of normal.[136]

Only minor changes were observed in other haematological and blood chemistry parameters. Vital signs, electrocardiogram, and pulmonary function were similar in the givinostat and placebo groups.[22, 132]

***QTc interval prolongation***

Givinostat can cause prolongation of QTc interval. However, no Fridericia corrected QT interval (QTcF) prolongation was recorded in either the givinostat or placebo groups, and other ECG parameters remained stable throughout the study.[136]

### B.2.9.2 OLE study

At December 2023 DCO, the mean actual duration of givinostat treatment was 1,177 days (standard deviation [SD] 453 days, range 26 to 2,259 days; mean actual duration 1,237 days in the givinostat group, 1,116 days in the delayed givinostat group, and 1,056 days in the naïve givinostat group).[135] The maximum givinostat exposure in the OLE was 6.1 years,[135] but 16 patients were previously treated for up to 4 years in Study 43, giving a maximum total exposure time of 10.1 years.[135, 168] Mean administration compliance was 98.6%, similar across all the givinostat treatment groups.[135]

No new safety signals have been identified from the ongoing OLE study. Results from the December 2023 DCO confirm that givinostat has a predictable and acceptable safety and tolerability profile consistent with EPIDYS and other studies of givinostat.[135]


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A summary of AEs from the December 2023 DCO (Safety analysis set [SAS] population) is provided in Table 35. Most AEs were mild to moderate, and no life-threatening AEs were reported.[135] The most frequently reported treatment-related AEs were blood triglycerides increased/hypertriglyceridaemia, diarrhoea, thrombocytopenia/platelet count decreased, blood thyroid stimulating hormone increased, abdominal pain and troponin increased.[135]

Two boys/young men died during the study; one due to a road traffic accident and one due to thoracic haemorrhage, which was not related to givinostat treatment.[135]

**Table 35: Summary of AEs | OLE study (SAS)**

| | Overall population (N=207) Events, subjects (%) |
|---|---|
| **AEs** | 2,793, 203 (98.1%) |
| **AEs leading to withdrawal from study** | 8 (3.9%) |
| **AEs leading to discontinuation of givinostat** | 9 (4.3%) |
| **Severity of AEs*** | |
| **Grade 1** | 2,294, 79 (38.2%) |
| **Grade 2** | 445, 83 (40.1%) |
| **Grade 3** | 50, 39 (18.8%) |
| **Grade 4** | 0 |
| **Grade 5** | 2, 2 (1.0%) |
| **Missing** | 2, 2 (1.0%) |
| **SAEs** | 64, 52 (25.1%) |
| **SAEs leading to discontinuation of givinostat** | 4 (1.9%) |
| **AEs leading to death** | 2 (1.0%) |
| **Treatment-related AEs*** | 623, 150 (72.5%) |
| **Treatment-related AEs leading to discontinuation of givinostat** | 4 (1.9%) |
| **Treatment-related SAEs** | 2, 2 (1.4%) |

*If a boy experienced more than one AE, the boy is counted once at the most severe or most related event; N = the number of subjects for the analysis set. Percentages (%) were calculated on the number of subjects.
Abbreviations: AE, adverse event; CRF, case report form; OLE, open-label extension; n, number of boys in the study population; SAS, Safety analysis set; SAEs, serious adverse event.
Source: DoF (Study 51 Clinical Study Report; Dec 2023 DCO).[135]

### B.2.9.3 Additional analysis of givinostat safety data

The company has conducted an additional limited assessment of safety outcomes in DMD patients who have become non ambulant while on treatment with either placebo or givinostat in Study 43, EPIDYS and the OLE (see Section B.2.6.7).[172]

A total of 34 boys/young men with DMD have become non-ambulant while participating in givinostat DMD clinical studies.[172] Overall, patients experienced fewer TEAEs following loss of ambulation compared with before loss of ambulation (Table 36), which is expected considering that the mean duration of exposure in this group of patients was approximately 60 months[172] and many of the more common TEAEs associated with givinostat (e.g. platelet count reductions) are most frequently experienced by patients within the first few months of


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treatment.[140] Review of platelet and triglyceride laboratory results and ECGs revealed no additional safety concerns in patients who lost ambulation while on treatment.[172]

These analyses show that loss of ambulation had no negative effects on the safety profile of givinostat.[172]

**Table 36: Overview of AEs in boys/young men who lost ambulation while receiving givinostat (safety set)**

| AE category | Givinostat overall (N=34) | |
|---|---|---|
| | Pre-loss of ambulation | Post-loss of ambulation |
| Number of AEs (events/patient years) | 572 (5.83) | 134 (2.19) |
| Number of boys/young men with AEs (n, %) | 34 (100%) | 29 (85.3%) |
| Number of SAEs (event/patient years) | 13 (0.13) | 7 (0.11) |
| Number of boys/young men with SAEs (n, %) | 11 (32.4%) | 6 (17.6%) |
| Number of severe AEs (event/patient years) | 11 (0.11) | 7 (0.11) |
| Number of boys/young men with severe AEs (n, %) | 9 (26.5%) | 6 (17.6%) |
| Number of AESIs (event/patient years) | 184 (1.88) | 35 (0.57) |
| Number of boys/young men with AESIs (n, %) | 31 (91.2%) | 19 (55.9%) |
| Number of AEs leading to discontinuation (event/patient years) | 0 | 1 (0.02) |
| Number of boys/young men with AEs leading to discontinuation (n, %) | 0 | 1 (2.9%) |
| Number of AEs leading to death (event/patient years) | 0 | 0 |
| Number of boys/young men with AEs leading to death (n, %) | 0 | 0 |
| Number of treatment-related AEs (n, %) | 194 (1.98) | 30 (0.49) |
| Number of boys/young men with treatment-related AEs (n, %) | 31 (91.2%) | 18 (52.9%) |

Notes: AEs with start date ≥date of first study medication intake are presented in this table; loss of ambulation is defined in the ISE SAP; considering the limited number of placebo patients under the defined analysis set, only givinostat patients have been included in this summary; AEs with start date ≥date of loss of ambulation are presented in the post-loss column; AEs with start date <date of loss of ambulation are presented in the pre-loss column; patient-years are calculated separately for pre- and post-loss of ambulation period.
Abbreviations: AE, adverse events; AESI, adverse event of special interest; N, number of boys in the study population, SAE, serious adverse event.
Source: DoF (Excerpt from D120 EMA responses 2024).[172]


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#### B.2.9.4 Safety conclusions

EPIDYS and the ongoing OLE study confirm that givinostat has a predictable safety profile, consistent with previous studies.[22, 132, 135] Treatment compliance is high and there have been no reported life-threatening AEs, or deaths related to givinostat treatment.[135] Givinostat was given in addition to the steroids in the placebo arm of the EPIDYS study, therefore AEs occur in both treatment arms. The additional givinostat-related AEs of diarrhoea, thrombocytopaenia and decreased platelet count, and increased blood triglycerides are generally manageable through dose modifications and typically occur more frequently in the first 3 months of treatment.[22, 132, 140]

### *B.2.10 Additional studies*

#### B.2.10.1 Study 43 (NCT01761292)

Study 43 was a Phase 1/2 proof of concept study for givinostat which led to further evaluation in the EPIDYS study (see Figure 11 for an overview of the givinostat clinical development programme).[22, 132] As patients from this study could enter the OLE, for completeness an overview of this study, including key efficacy and safety results is presented in Appendix M.6.

### *B.2.11 Ongoing studies (in addition to the OLE study)*

Refer to Figure 11 for an overview of the givinostat clinical development programme.

#### B.2.11.1 ULYSSES (Study 50, NCT05933057)

ULYSSES (Study 50) is an ongoing Phase 3 randomised, double-blind safety and efficacy study in non-ambulant boys and male adolescents aged 9 to 17 years who have not previously received givinostat.[143] It is planned that 138 boys will be randomised 2:1 to givinostat or placebo and treated for 18 months. The primary endpoint is change of PUL total score at 18 months of treatment with givinostat versus placebo.[143] Secondary endpoints included change from baseline of PEF percent predicted (PEF%p) at 18 months, change from baseline of FVC percent predicted (FVC%p) at 18 months, cumulative loss of PUL total score over 18 months, type, incidence, and severity of AEs and change from baseline vital signs, clinical laboratory tests, ECG and echocardiogram, as well as time to assisted ventilation and rate of respiratory infection.[143] The study is anticipated to finish in mid-2028.

#### B.2.11.2 Study 52

Study 52 is a Phase 2, open-label, safety and PK study in ambulant boys with DMD aged from 2 years to <6 years.[146] The study will follow 18 boys for 12 months with an extension phase up to 24 months. The study is anticipated to finish in 2029.


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## *B.2.12 Interpretation of clinical effectiveness and safety evidence*

### B.2.12.1 Principal findings from EPIDYS and the OLE study

DMD is progressive disease that has a debilitating impact on muscles across the body, resulting in substantial and wide-ranging functional decline. Givinostat delays disease progression and loss of ambulation,[22, 132, 139] thereby potentially giving boys with DMD and their families an opportunity to retain functional abilities for longer. Compared with ECM, givinostat slows decline in the ability to climb four stairs, maintains the ability to run, jump, hop and rise from the floor/a chair for longer, slows decline in muscle strength in both lower and upper limbs, slows fat infiltration in muscles, and delays loss of ambulation.[22, 132, 139] The ITCs enabled comparison between patients treated with givinostat in EPIDYS with a real-world population of patients receiving ECM in UK clinical practice. The analyses suggest that DMD patients treated with givinostat are likely to experience a significant delay in both ambulatory and non-ambulatory function, beyond that observed in the EPIDYS trial (Section B.2.8.4). Givinostat is also anticipated to have positive effects for boys and young men irrespective of disease stage, including those who become non-ambulant after starting treatment.

*Impact of givinostat on ambulation and muscle strength*

In EPIDYS, givinostat provided a statistically significant and clinically meaningful slowing of the decline in ability to climb four stairs compared with placebo,[22, 132] indicative of a reduction in the rate of disease progression. The geometric LS mean ratios for the log transformed 4SC results at 18 months versus baseline were 1.27 (95% CI 1.17 to 1.37) in the givinostat group versus 1.48 (95% CI 1.32 to 1.66) in the placebo group (ratio 0.86; 95% CI 0.75 to 0.99, p=0.035).[22, 132] Non-log-transformed data showed a reduction of ~40% in the decline in 4SC over 18 months for givinostat vs. placebo (a 1.78 seconds smaller decline with givinostat).[22, 132] The slower decline in ability to climb four stairs for givinostat compared with placebo is clinically relevant and is expected to lead to improved participation in physical and social activities of daily life, and a prolonged ability to walk.

Boys who received givinostat were also more likely to maintain the ability to do other important activities for longer, including running, jumping, hopping and rising from a chair, compared with those who received placebo.[22, 132] As described in Section B.1.3.6, boys with DMD report that they would greatly value being able to walk, run and play sports with their friends and siblings for longer. Cumulative loss of function was numerically lower with givinostat than with placebo (2.14 fewer items failed over 18 months; p=0.0202); this is important because a loss of 2 NSAA items predicts clinically meaningful disease progression and loss of ambulation in a functionally declining group, such as the boys in EPIDYS.[137]

Consistent with the benefits seen on daily activities, muscle strength – evaluated by knee extension or elbow flexion – showed numerically less decline with givinostat than with placebo at 18 months[22, 132] Treatment with givinostat also reduced fat infiltration in thigh muscles by approximately 30% – a benefit which is considered to be clinically meaningful, because increased VL MFF inversely correlates with muscle function, daily activities and predicts loss of ambulation.


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*Impact of givinostat beyond ambulatory ability*

Importantly, the functional and histologic benefits seen in muscle groups associated with walking[22, 132] are expected to be replicated in other muscle groups, because givinostat's mechanism of action is such that acts on all muscles, not just those associated with walking. Amongst other potential positive impacts, this broader activity can potentially slow the decline in muscles used for transferring to a wheelchair, for hand-to-mouth transfer, for fine motor finger control and for breathing. This has been confirmed by clinical experts consulted by the Company,[20] and is already being demonstrated in data from the OLE study which includes upper limb endpoints. Maintaining upper limb function as long as possible is really important because young men with DMD report that losing strength in their arms limits their independence more than their legs (see Section B.1.3.6). Preliminary results from the small number of boys who became non-ambulant after starting givinostat are supportive of the efficacy of givinostat in this patient-group.[172]

Givinostat is also anticipated to provide benefits regardless of age or underlying DMD mutations.

*Long-term impact for boys and young men with DMD*

Longer-term results of the ongoing OLE study support the results from EPIDYS and suggest that givinostat delays the occurrence of major disease milestones, including loss of ambulation. At the December 2023 DCO, 37.7% (n=78) of the Overall population (N=207), had lost ambulation.[135] The median age at loss of ambulation was 16.7 years in the givinostat group, considerably higher than the median age expected in a DMD population treated with CS only (11 years 8 months in a 2022 analysis of data from the UK North Star Network database).[73]

While givinostat does not prevent the major challenges associated with moving from paediatric to adult DMD services (see Section B.1.3.6), by potentially delaying disease progression, it does mean that this is more likely to occur when boys have better function and abilities.[20]

*Givinostat is well tolerated with a predictable safety profile*

EPIDYS and OLE study safety results demonstrated a predictable and manageable safety profile for givinostat.[22, 132, 135] In EPIDYS, nearly all boys (95%) completed the study, and treatment compliance was high.[22, 132] Most AEs observed with givinostat were mild to moderate in severity, they appeared more frequently in the first 3 months of treatment and were generally manageable through dose reduction or interruption.[22, 132, 140] No boys died during EPIDYS and no severe or serious AEs were considered related to the study drug or led to withdrawal.[22, 132] The most common AEs (diarrhoea, abdominal pain, low platelet levels, and high levels of triglycerides) appear most frequently in the first 3 months of treatment and are generally manageable through dose management.[22, 132, 135, 139, 140] Initial results from the small number of boys who became non-ambulant after starting givinostat show no negative effect of the loss of ambulation on givinostat's safety profile.[172]

Taken together, the primary, key secondary endpoint and AE data from EPIDYS and ongoing OLE study show a grouping of effects that consistently support the long-term


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efficacy of givinostat in delaying loss of muscle function in boys and young men with DMD.[22, 132, 135, 139, 140]

### B.2.12.2 Strengths and limitations of the clinical evidence base

**Strengths of the evidence base**

Phase 3 EPIDYS outcomes provide confirmatory evidence of givinostat's efficacy, as previously indicated by pre-clinical mouse muscle outcomes and Phase 2 study results.[17, 18, 22, 132]

- **Recruited a broad population of ambulant boys |** Compared with those benefitting from mutation-specific antisense therapies, EPIDYS recruited a broad population of boys with DMD, with a wide range of baseline VL MFF values, even within the Target ITT population.[22, 132] This population was expected to show sufficient decline with placebo but not to be at risk of a sudden loss of ambulation. The enrichment was effective, with only one boy (receiving placebo) losing ambulation.
- **Flexible dosing regimen to maximise efficacy |** Boys received a flexible-dose regimen aimed at maximising efficacy, starting with a high dose that was reduced if treatment was not tolerated. The protocol was amended to lower the starting dose, but the *post hoc* ANCOVA suggested that the treatment effect was not affected by the change in treatment regimen.
- **Unprecedented Phase 3 randomisation period |** The 18 month double-blind study length was chosen to demonstrate a functional benefit of givinostat compared with the ECM only group in the study population.[22, 132] By contrast, the treatment period in the Phase 3 ataluren study was 48 weeks.[5]
- **One of the largest Phase 3 RCTs in DMD |** EPIDYS included 179 boys with DMD.[22, 132]

EPIDYS included validated, objective and clinically-relevant outcomes and demonstrated clinically meaningful differences versus placebo (both in addition to ECM).[22, 132] The study met its primary endpoint, with significantly smaller decline in 4SC results with givinostat than with placebo in ambulant boys with DMD. No new safety signals were detected, and a high proportion of boys completed the study. The risk of unmasking of study personnel due to permitted dose reductions (mainly in response to AEs) was mitigated by having different people assessing efficacy from those who reviewing safety data. Furthermore, dose adjustments were most often in response to platelet or triglyceride abnormalities, and laboratory results were not communicated to sites until 24 to 48 hours after these efficacy assessments.[22, 132]

MRS evidence from EPIDYS added weight to previous histological findings, showing that there was numerically less fat infiltration in the vastus lateralis at 18 months with givinostat than with placebo.[22, 132] In a DMD mouse model, givinostat increased cross-sectional myofibre area and decreased inflammatory infiltrate and fibrotic scars,[17] and in Study 43 (Section B.2.10.1), the drug increased the fraction of muscle tissue and reduced the fraction of fibrosis, necrosis, and fatty replacement in brachial biceps biopsy samples.[18] This evidence indicates that givinostat works across both lower and upper limb muscle groups.


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Overall, the results demonstrate that givinostat positively impacts the trajectory of the disease and preserves muscle mass and function compared with ECM.

The ongoing OLE study is evaluating long-term safety and efficacy, and the full givinostat development programme is gathering additional evidence across the whole DMD treatment paradigm. Results from the ongoing OLE study (Dec 2023 DCO) show that treatment compliance has remained high, and efficacy and safety results that are consistent with those seen in EPIDYS, for boys continuing (n=119; maximum givinostat exposure of up to 10 years) or starting (n=88) givinostat treatment. Median age at loss of ambulation was 16.7 years,[135] higher than expected in boys and young men with DMD treated with CS alone.[73]

**Potential limitations of the evidence base**

Only a small number of boys have became non-ambulant after starting givinostat during Study 43, EPIDYS and the ongoing OLE study (Section B.2.3.5).[172] The full givinostat clinical development programme (Section B.2.3 and Figure 11) will eventually provide evidence from a broad population and in a broad range of patients, including younger boys and those with early disease, boys with all types of genetic mutations, and non-ambulant boys and young men. Givinostat's underlying mechanism of action (Section B.1.2) and preclinical[17] and clinical results[18, 22, 132] to date suggest it is expected to be efficacious regardless of age, disease phase and underlying DMD mutations. Furthermore, clinical experts consulted by the company have confirmed that there is no clinical rationale for expecting its efficacy to be different in muscles used for walking versus other muscles in the body, such as those involved in hand to mouth function, respiration and cardiac function.[20]

In EPIDYS, almost all boys were White and none of the study centres was in Africa or Asia, although this limitation probably makes the population more generalisable to the UK.[22, 132] Additionally, only males were recruited into the study.[22, 132] DMD is an X-linked recessive neuromuscular disorder that predominantly affects males;[11] however, further studies are needed to establish the possible effect of givinostat on female carriers, who can manifest the disease in rare cases and often have a very different presentation to males.[189]

Despite being one of the largest Phase 3 clinical RCTs in DMD, it was not possible to recruit sufficient patients to power all of the key secondary endpoints, due to the rarity of DMD.[22, 132] Therefore the finding that EPIDYS secondary endpoints did not reach formal significance after correction for multiplicity was therefore expected; this is especially the case when the commonly applied alpha control mechanisms (which include the Hochberg procedure) do not account for the correlation between the endpoints included.[22, 132] However, the results are supported by the *post hoc* permutation test analysis (Section B.2.6.2), which showed that the overall constellation of observed positive results were highly unlikely to have happened by chance.[22, 132]

Another possible limitation of the study is that, due to the protocol amendment (which was conducted without unmasking) some boys started the study on a lower dose of givinostat.[22, 132] This dose reduction did not affect efficacy but did improve overall safety,[22, 132] and aligns with practice guidelines recommending similar dose reductions for CS to manage AEs in DMD.[190]


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# B.3 Cost effectiveness

## *B.3.1 Published cost-effectiveness studies*

An economic SLR was conducted to identify all published economic models relevant to treatments in the management of patients with DMD. Searches were conducted through May and June 2024, and updated in November 2024. The methodology undertaken is described in Appendix G, which details the search strategy, eligibility criteria applied, and full list of identified references. A total of 14 publications were included in the economic SLR from the database searches, grey literature searches, and hand searching.

Appendix G details the 14 identified publications. Of these, four publications considered a UK perspective (Broomfield et al. 2024, the ataluren submission to NICE, the ataluren submission to the Scottish Medicines Consortium (SMC), and Landfeldt et al. 2017 and are summarised in Table 37.[7, 123, 191, 192] Note: the ataluren cost-effectiveness model submitted to NICE and detailed in Table 37 superseded previous modelling work involving cost-consequence modelling submitted to NICE, the details of which are not presented here. The ongoing vamorolone NICE submission (GID-TA11135) is also summarised in Table 37; this was not identified in the SLR as the final documents relevant to this appraisal have not yet been published.[130]

Across the five studies described in Table 37, three used multi-state transition model structures and two used partitioned survival model structures. Whilst the ataluren submissions to NICE and SMC used the partitioned survival model structure, health states aligned with other identified studies, and feedback from the Committee in the NICE appraisal indicated that the partitioned survival model structure may be lacking sufficient granularity to capture key aspects of disease progression. All studies included health states defined by ambulatory status and/or ventilation status. Of the four studies which reported a time horizon, all considered a lifetime horizon ranging from 50- to 70-years. Cycle lengths were reported in three studies and reflected one month, 3-months, and 12-months. These findings are consistent with the non-UK studies reported in Appendix G.


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**Table 37: Summary list of published cost-effectiveness studies**

| Study | Year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| NICE[130]<br><br>Ongoing appraisal of vamorolone for treating DMD (GID-TA11135) | Ongoing | **Objective:** to perform a cost-effectiveness analysis of vamorolone compared to ECM without vamorolone for the treatment of people with DMD aged 4 years who are glucocorticoid-naïve<br><br>The perspective was the UK NHS and PSS<br><br>The model structure was based on the Project HERCULES CEM; a cohort-based Markov model structure with disease-specific health states. Ambulatory health states: early ambulatory, late ambulatory, and transfer. Non-ambulatory health states: HTMF and no ventilation, HTMF and night-time ventilation, no HTMF and no ventilation, no HTMF and night-time ventilation, and full ventilation<br><br>A lifetime time horizon (50-years) was considered with 1-month cycles<br><br>Health state utilities and caregiver utilities are sourced from the Project HERCULES BOI study and Landfeldt et al. 2014[45, 56, 193]<br><br>Transitions from the Project HERCULES natural history are used in the model for vamorolone. Comparative efficacy are based on McDonald et al. 2018[187] | 4.1 | Note: this appraisal is ongoing. Results are from the first Committee meeting<br><br>**EAG corrected company base case**<br>Total QALYs<br>Prednisone 10.567<br>Deflazacort 10.657<br>Vamorolone 12.771 | Costs are redacted | ICERs are redacted |


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| Study | Year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| | | Resource utilisation costs associated with AEs are taken the NHS references costs. Treatment costs are taken from the BNF.[194, 195] Remaining costs are taken from UK published literature (including the Project HERCULES BOI study and Landfeldt et al. 2014)<br><br>Costs and benefits were discounted at 3.5% per annum. A scenario analysis explores 1.5% | | | | |
| Broomfield et al. 2024[191] | 2023 | **Objective:** To assess the impact of a failure to account for study heterogeneity in a NHM on the results of a CEA for a hypothetical treatment for DMD<br><br>Perspective not reported<br><br>Five-stage multi-state natural history model. Health states: (1) early ambulatory; (2) late ambulatory; (3) earl non-ambulatory; (4) late non-ambulatory; (5) Death<br><br>Three methods for predicting disease progression rates/probabilities that account for the study heterogeneity in the data were compared to a method that simply grouped the data together with no adjustment and an assumption-based method. These three methods were a one stage frailty model a two-stage model assuming proportional baseline hazards and a two-stage model assuming stratified baselines | NR | Difference in QALYs by method:<br>Assumption based: 0.772<br>No adjustment: 0.325<br>One-stage frailty: 0.307<br>Two-stage proportional: 0.304<br>Two-stage stratified: 0.324 | Difference in costs by method:<br>Assumption based: £1,517,000<br>No adjustment: £1,520,000<br>One-stage frailty: £1,427,000<br>Two-stage proportional: £1,399,000<br>Two-stage stratified: £1,229,000 | ICERs by method:<br>Assumption based: £1,964,000<br>No adjustment: £4,672,000<br>One-stage frailty: £4,648,000<br>Two-stage proportional: £4,605,000<br>Two-stage stratified: £3,798,000 |


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| Study | Year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| | | Lifetime horizon<br><br>Utilities from Landfeldt et al. 2017[192]<br><br>Costs and QALYs were discounted at 3.5% | | | | |
| Landfeldt et al. 2017[192] | 2017 | **Objective:** to develop a cost-effectiveness analysis of a hypothetical treatment for DMD vs. standard of care based on the DMDSAT and compare it with two alternative model structures<br><br>The base case perspective was a UK healthcare perspective. Additional SA analysed a wider UK societal perspective<br><br>Three cost-effectiveness Markov models were used:<br>• Model I used 25 health states based upon DMDSAT score (DMDSAT score: 23; DMDSAT score: 22; DMDSAT score: 21; DMDSAT score: 0; and dead)<br>• Model II used 5 health states based on ambulation status (early ambulatory (aged approx. 5-7 years); late ambulatory (aged approx. 8-11 years); early non- ambulatory (aged approx. 16+ years); and dead)<br>• Model III used 4 health states based on ventilation status (no ventilation support; night-time ventilation support; night- and daytime ventilation support; and dead) | 5 (hypothetical cohort) | **Treatment**<br>Model I:<br>Patients 8.13<br>Caregivers 12.93<br>Model II:<br>Patients 7.96<br>Caregivers 12.89<br>Model III:<br>Patients 6.93<br>Caregivers 12.72<br><br>**Standard of care**<br>Model I:<br>Patients 7.07<br>Caregivers 12.80<br>Model II:<br>Patients 7.17<br>Caregivers 12.82<br>Model III:<br>Patients 5.96<br>Caregivers 12.66 | **Treatment**<br>Model I:<br>Healthcare £1,737,960<br>Societal £2,117,140<br>Model II:<br>Healthcare £1,768,370<br>Societal £2,171,380<br>Model III:<br>Healthcare £1,809,160<br>Societal £2,232,890<br><br>**Standard of care**<br>Model I:<br>Healthcare £217,510<br>Societal £624,240 | All results are ICERs per QALY for a hypothetical treatment for DMD<br>vs. standard of care.<br><br>**Base case**<br>Model I:<br>Healthcare £1,442,710<br>Societal £1,266,510<br>Model II:<br>Healthcare £1,939,590<br>Societal £1,760,650<br>Model III:<br>Healthcare £3,574,770<br>Societal £3,121,890 |


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| Study | Year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| | | In all models, a lifetime horizon was used (until natural death or until aged 100) and cycle length was 12 months<br><br>Patient utilities were derived using HUI. Caregiver utilities were assessed by EQ 5D-3L. Utilities were estimated from a previous cross-sectional, observational study[56]<br><br>Transition probabilities were derived from probability of disease progression – patients could either remain in their current state, progress to worse state or die. In model I, a linear decline in the rate of progression was assumed. Model II assumed a linear progression based on age (as defined in DMD clinical care guidelines by Bushby et al. 2010).[75] Model III derived state transition probabilities from the mean time to ventilation support based on clinical experience and published evidence<br><br>In all models it was assumed that patients enter in the least bad state (DMDSAT 23; early ambulatory; no ventilation support)<br><br>Model input data were collated through a targeted literature review in PubMed and Web of Science, and from DMD experts. Costs were converted from US dollars to GB pounds and inflated from 2012 to 2015 values using consumer price indices. Costs were collected in a previous cross-sectional, observational study.[56] Data for mortality for patients younger than 18 | | | Model II:<br>Healthcare<br>£244,120<br>Societal<br>£663,500<br>Model III:<br>Healthcare<br>£284,640<br>Societal<br>£713,840 | **<u>Scenario analyses</u>**<br>ICER range:<br>Model I:<br>£1,324,740–<br>£3,313,550<br>Model II:<br>£1,479,360–<br>£2,131.650<br>Model III:<br>£2,394,430–<br>£4,064,600 |


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| Study | Year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| | | was taken from age-specific UK male general population mortality rates from UK ONS. After the age of 18, it was assumed that 50% of patients would die by age 25 and an equal yearly probability was used and extended to age 35. Patients surviving beyond 35 years were expected to have a 15% increase in mortality per year<br><br>Costs and QALYs were discounted at 3.5% per annum | | | | |
| SMC 2016[123] | 2016 | **Objective:** Cost-utility analysis of ataluren plus BSC vs. BSC alone for the treatment of DMD in ambulatory patients aged ≥5 years from the perspective of NHS Scotland<br><br>A partitioned survival approach was adopted, with several health states. Patients entered the model in an ambulatory state. Subsequent states were loss of ambulation (fully wheelchair bound), predicted FVC greater or less than 50%, FVC<1L, and death<br><br>The time horizon and cycle length used in the model are not stated<br><br>Clinical data was sourced from a clinical trial and extrapolated (study ID PTC124-GD-007-DMD).[196] Published sources were used to estimate time to loss of ambulation curves, transition probabilities from non-ambulatory health state to ventilation assistance and/or | 8.5 | **Base case**<br>Incremental QALY for ataluren vs. BSC 6.089 | **Base case**<br>Incremental cost for ataluren vs. BSC £4,891,213 | **Base case**<br>£793,498/QALY for ataluren vs. BSC |


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| Study | Year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| | | scoliosis health states for the comparator, and the transition to the death health state for BSC<br><br>Utility estimates were taken from published sources and were treatment specific for the non-ambulatory health states. Analysis also included caregiver utilities in both arms<br><br>Costs for medicines, disease management and surgery were included. No costs were included for the monitoring and administration costs for ataluren. Their source was not stated<br><br>Discounting was increased to 6% per annum in sensitivity analysis but the base case was not stated in the base case | | | | |
| NICE 2015[7] | 2015 | **Objective:** Cost-utility analysis of ataluren plus BSC vs. BSC alone for the treatment of DMD in ambulatory patients aged ≥5 years<br><br>The perspective was the UK NHS and PSS<br><br>Semi-Markov model, partitioned survival models in each health state (ambulatory, non-ambulatory; FVC above 50%, below 50% and below 30%). Six health states which represented the progression of DMD from the ambulatory phase to the non-ambulatory phases and death<br><br>70-year time horizon with 3-monthly cycles | All patients start in ambulatory state and are assumed to be 2 years of age | NR | NR | <£100,000 |


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| Study | Year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| | | Survival curves from STRIDE (ataluren), propensity score matched to CINRG DNHS (BSC) for age at loss of ambulation, age at predicted FVC <50% and age at predicted FVC <30%, were used to represent the rate of disease progression in patients receiving ataluren. Additional treatment benefits were based on a Delphi panel<br><br>Direct and indirect health state costs were taken from Landfeldt et al. 2014, ONS and OECD. NHS reference costs were used for surgery & surgery follow-up costs<br><br>Utilities for patients were obtained from a Delphi panel study published in Landfeldt et al. 2020.[197] Utilities for caregivers were taken from Landfeldt et al. 2017<br><br>Costs and benefits were discounted at 3.5% per annum | | | | |

Abbreviations: BSC, best supportive care; DMD, Duchenne muscular dystrophy; DMDSAT, Duchenne muscular dystrophy Functional Ability Self-Assessment Tool; DTVAD, Destination therapy ventricular assist device; EAG, External Assessment Group; ECM, established clinical management; EQ-5D-3L, Euro-QoL-5 Dimensions-3 Levels; FVC, forced vital capacity; FVC<1L, FVC <1 litre; GB, Great Britain; HF, heart failure; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MM, medical management; OECD/ONS, Office of National Statistics; PSS, personal social services; QoL, quality of life; QALYs, quality adjusted life year; SA, sensitivity analyses; UK, United Kingdom; US, United States; VAD, ventricular assisted device; vs., versus.


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## *B.3.2 Economic analysis*

This submission utilises the output from Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis), a unique initiative, led by Duchenne UK, to develop tools and evidence to support HTA and reimbursement decisions for new treatments for DMD. One of the key outputs from this initiative is the development of a cost-effectiveness model (CEM) building on the natural history model (NHM) as presented in Broomfield et al. 2024.[191]

The Project HERCULES CEM is the most relevant structure to inform this appraisal due to the wide network of stakeholders – including clinical experts, carers, and patients - involved in the model development. This multi-stakeholder approach ensures that the model structure reflects the most important aspects of the patient and treatment pathway in DMD. Additionally, this structure has been utilised in the ongoing NICE appraisal for vamorolone for treating DMD in patients ≥4 years, where the Committee concluded that the overall model structure was appropriate for decision making.[130]

The selection of a state transition model defined by ambulatory and ventilation health states aligns with the results of the SLR; three of the five identified UK studies described in Table 37 used a multi-state transition model and all five identified UK studies used health states defined by ambulatory and ventilation status. The model is described in further detail throughout this Section.

### B.3.2.1 Patient population

In line with the final NICE scope for this appraisal, the CEM considers people with DMD six years of age and older who are ambulant when they initiate treatment.[198] This is a subpopulation of the anticipated GB marketing authorisation for givinostat.

The CEM assumes a starting age of six years, aligned with the patient population and the population included in the EPIDYS study.[22] Weight, height, and body surface area (BSA) for boys aged 6–18 years are sourced from the Royal College of Paediatrics and Child Health data (see Table 38).[199]


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**Table 38: Weight, height, and BSA for boys aged 6–18 years[199]**

| Age (years) | Weight (kg) | Height (cm) | BSA ($m^2$) |
|---|---|---|---|
| 6 | 22.00 | 119 | 0.85 |
| 7 | 24.25 | 125 | 0.92 |
| 8 | 27.00 | 131 | 0.99 |
| 9 | 30.00 | 136 | 1.06 |
| 10 | 33.00 | 141 | 1.14 |
| 11 | 36.25 | 146 | 1.21 |
| 12 | 40.50 | 151 | 1.30 |
| 13 | 46.00 | 159 | 1.43 |
| 14 | 52.50 | 166 | 1.56 |
| 15 | 58.25 | 171 | 1.66 |
| 16 | 62.75 | 175 | 1.75 |
| 17 | 66.00 | 177 | 1.80 |
| 18+ | 83.60 | 178 | 2.03 |

Abbreviations: BSA, body surface area; cm, centimetres; kg, kilograms; m, metres.

### B.3.2.2 Model structure

The Project HERCULES CEM uses a cohort multi-state transition model structure with disease-specific health states and was developed in Microsoft Excel.

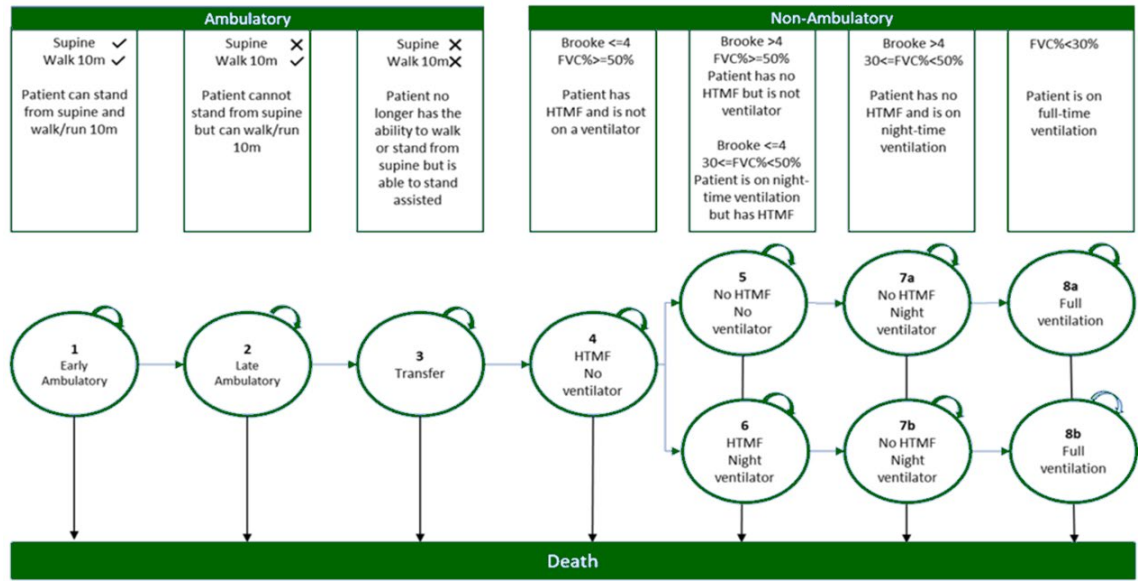
The Project HERCULES model structure was developed using previously identified health states in the published literature; input from clinicians, academics, patients, and caregivers; and reflects outcomes commonly collected in clinical trials and real-world practice. The process for defining model health states is described below:

- A targeted literature review (TLR) of previous natural history studies and functional scales used in DMD was performed in MEDLINE. This identified existing health state definitions, key milestones in disease progression, and outcomes captured in clinical trials.
- Following the TLR, preliminary health states were defined. These were based on the conventional view of health states in DMD, such as those proposed by Bushby et al. 2010.[75] These health states were presented for stakeholder input, obtained through an advisory board and follow-up questions with two neuromuscular specialists.
- Final health states were validated with a group of clinical experts with extensive experience of treating patients with DMD.

The Project HERCULES model health states are well-validated and no changes to the model structure have been considered for the CEM presented in this submission. The model structure is presented in Figure 34. The structure adopts a cohort multi-state transition model, comprising ambulatory and non-ambulatory health states, plus an intermediate "transfer" health state, and death.


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**Figure 34: Model schematic**




Abbreviations: FVC, forced vital capacity; HTMF, hand-to-mouth function; m, metres.

The CEM assumes all patients start in health state (1) i.e. the early ambulatory health state – reflecting the inclusion criteria in the EPIDYs clinical trial.

The health states "(1) early ambulatory", "(2) late ambulatory", and "(3) transfer" form the ambulatory health states. Patients can transition from the health state (1) to (2) or death and from the health state (2) to (3) or death. Table 39 defines the ambulatory health states in terms of functionality ability and function lost.

**Table 39: Definition of ambulatory health states**

| | Early ambulatory | Late ambulatory | Transfer |
|---|---|---|---|
| Health state, N | 1 | 2 | 3 |
| Functional ability | Stand from supine<br>Walk or run 10m<br>Stand | Walk or run 10m<br>Stand | Stand |
| Function lost | NA | Stand from supine | Stand from supine<br>Walk or run 10m |

Abbreviations: N, number; NA, not applicable.

Patients can transition from the health state (3) to non-ambulatory health states. The health states "(4) HTMF, no ventilator", "(5) no HTMF, no ventilator", "(6) HTMF, night ventilator", "(7a) no HTMF, night ventilator", "(7b) no HTMF, night ventilator", "(8a) full ventilation", and "(8b) full ventilation" form the non-ambulatory health states. Patients transitioning from the health state (4) are split into one of two pathways depending on which function (HTMF or independent breathing) is lost first. For example, patients transition from the health state (4) to (5) if HTMF function is lost first or to (6) if independent breathing at night is lost first. Patients cannot transition between (5) and (6). In health states (7a) and (7b), patients have lost HTMF and require night time ventilation. In health states (8a) and (8b), patients require full-time ventilation. The distinction between health states (8a) and (8b) is the route by which


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the patient cohort reached these states. Whilst transition probabilities in the CEM vary according to each pathway, the utilities and costs accrued in health states (7a) and (8a) are aligned with (7b) and (8b), respectively. Table 40 defines the non-ambulatory health states in terms of Brooke scale of upper extremity function (Brooke score) and the FVC score.

The Brooke and FVC score capture the key determinants of utilities and cost in the non-ambulatory states, namely, the ability to self-feed and the requirement for ventilation. There is a positive correlation between the two metrics; McDonald et al. 2018 reported pFVC% (FVC percent predicted) by Brooke score and demonstrated that loss of upper extremity function correlated strongly with progressive loss of pulmonary function.[187]

**Table 40: Definition of non-ambulatory health states**

| | HTMF, no ventilation | HTMF, night ventilation | No HTMF, no ventilation | No HTMF, night ventilation | Full ventilation |
|---|---|---|---|---|---|
| Health state, N | 4 | 5 | 6 | 7a, 7b | 8a, 8b |
| HTMF (Brooke score) | ≤4 | ≤4 | >4 | >4 | >4 |
| Pulmonary function (FVC) | >50% | ≥30% and ≤50% | >50% | ≥30% and ≤50% | <30% |
| Description | Ability to self-feed, not on a ventilator | Ability to self-feed and is on night-time ventilation | Unable to self-feed, not on a ventilator | Unable to self-feed and is on night-time ventilation | Full-time ventilation |

Abbreviations: FVC, forced vital capacity; HTMF, hand-to-mouth function; N, number.

The NICE reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be long enough to reflect all important differences in costs or outcomes between the technologies.[200] As DMD is a lifelong illness, and treatment with givinostat can be given across a patient's lifetime, a lifetime horizon is applied. Therefore, the CEM considers a time horizon of 70-years; at this point less than 0.1% of patients are alive in the ECM arm. The impact of a 50- and 60-year time horizon are explored in scenario analyses.

A one-month cycle is implemented in the CEM, aligning with the most granular output from the Project HERCULEs NHM. This cycle length enables the most accurate aggregation of utilities and costs across the time horizon. A half-cycle correction is applied in the CEM.
In line with the NICE reference case, the CEM considers all health effects, including for patients and caregivers, for outcomes. Caregiver HRQoL is highly relevant to this decision problem - because of the devastating disease progression, patients with DMD inevitably transition towards a state of total dependency, requiring wheelchairs for mobility from their early teens and ventilation support for survival in more advanced stages of the disease.[45] Many patients with DMD also suffer from mental health comorbidities, such as autism spectrum disorder and obsessive-compulsive disorder. Therefore, patients progress to requiring 24-hour care, often provided by informal caregivers. The Department of Health and Social Care has described an informal/unpaid carer as someone who provides unpaid help to a friend or family member needing support, perhaps due to illness, older age, disability, a


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mental health condition or an addiction, as long as they are not employed to do so.[201] Providing this level of care has a detrimental effect on the mental and physical health of caregivers, as well as on their day-to-day activities and professional life, which worsens as the disease progresses. This quote from a parent of a son with DMD contextualises some of the impact on HRQoL for parents:

**"When my son was diagnosed with Duchenne Muscular Dystrophy my mental health hit rock bottom. It has never recovered to pre-diagnosis levels. For the first ten years I was in a profound state of grief. Grieving for the death of a life I thought my son was going to have. And grieving for his short, disabled life. I have now come through that tunnel of grief: and what am I facing? My son is now 17, non-ambulant. I am in constant fear of his heart failing, of his breathing getting worse. And I still grieve every single day for the loss of ambulation, the loss of his arm strength, seeing the devastating impact on his loss of independence, and low feelings of self-esteem"**

*Parent of a son with DMD.*[84]

In the NICE appraisal of ataluren for treating DMD with a nonsense mutation in the dystrophin gene (HST22), the patient experts described the significant effect of DMD on caregivers.[7] It was explained that patients with DMD need assistance with everyday tasks, such as getting dressed and getting out of bed. It was also described how caregiving becomes more challenging once someone stops being able to walk and the disease progresses. It was highlighted that delaying the loss of the ability to walk and maintaining upper limb function are very important to patients with DMD and caregivers. As part of this appraisal, the Committee concluded that DMD has a substantial impact on both patients with the condition and caregivers. As part of the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135), the significant impact of the disease on caregivers has also been a key discussion topic.[130] Following the first Committee meeting, the Committee concluded that DMD has a substantial effect on patients with the condition, as well as their families and carers.

Therefore, when assessing the value of therapies for DMD, it is important to consider the health impact of patients and the informal caregivers – as agreed in previously published NICE appraisals in DMD and the Spillovers in Health Economic Evaluation and Research (SHEER) Task Force.[202]

In line with the NICE reference case, the CEM adopts a UK NHS and personal social services (PSS) perspective for costs. Many caregivers to patients with DMD terminate their employment or reduce their working hours to find the time needed to care for their children, and those who do continue to work have markedly impaired productivity with high levels of absenteeism.[45] Therefore, a scenario explores a broader costing perspective and considers the impact of societal costs.

Costs are discounted at 3.5% per annum in line with the NICE reference case. Outcomes are discounted at 3.5% per annum for the first 30 years. After this time point, in line with the guidance presented in the HM Treasury Green Book - which states that the discount rate applied to QALYs should reduce over time when evaluating therapies with benefits which extend over 30-years – outcomes are discounted at 1.5% per annum.[203]


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Although the discount rates applied to outcomes in the base case deviate from the NICE reference case, the non-reference case discount rate of 1.5% is highly relevant in this submission. Givinostat meets two of the three criteria specified in the NICE Manual for non-reference discounting i.e., givinostat is for people who have a very severely impaired life and the benefits of givinostat are likely to be sustained over a very long period. Although, givinostat does not restore patients to full or near-full health (the final criteria), givinostat extends the time in which patients maintain in earlier health states which are associated with improved HRQoL. Therefore, a scenario explores a discount rate for outcomes of 1.5% per annum across the model time horizon. As discussed in the HM Treasury Green Book, costs remain discounted at 3.5% to balance the impact of inflation over time.

Table 41 summarises the features of the economic analysis.


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**Table 41: Features of the economic analysis**

| | Previous appraisals | | Current appraisal | |
|---|---|---|---|---|
| **Factor** | **HST22**[7] | **ID4024 (ongoing)**[130] | **Chosen values** | **Justification** |
| Time horizon | 70-years (lifetime) | 50-years (lifetime) | 70-years (lifetime) | DMD is a lifelong illness, and treatment with givinostat can be given across a patient's lifetime. Therefore, a lifetime horizon is applied – in line with the NICE reference case.[200] At 70-years less than 0.1% of patients are alive in the ECM arm |
| Cycle length | 3-months | One month | One month | This aligns with the most granular output from the Project HERCULEs NHM and was used to enable the most accurate aggregation of utilities and costs across the time horizon[191] |
| Perspective on costs | UK NHS/PSS | UK NHS/PSS | UK NHS/PSS | NICE reference case |
| Perspective on outcomes | Patients and carers | Patients and carers | Patients and carers | NICE reference case |
| Source of health state transitions | **Best supportive care:** CINRG<br>**Ataluren vs. best supportive care:** STRIDE, Study 019, and CINRG | **Steroids:** Project HERCULES NHM and VISION-DMD<br>**Vamorolone vs. steroids:** VISION-DMD and CINRG | **ECM:** Project HERCULES NHM, UK real-world data, and clinical opinion<br>**Givinostat vs. ECM:** EPIDYS, OLE study, and UK real-world data | The Project HERCULES NHM provides a set of transition intensities to inform the natural history of DMD for ECM. UK real-world data supplement the NHM to align predicted outcomes with UK clinical practice<br>Unanchored MAICs were conducted to estimate the relative efficacy of givinostat vs. ECM. This approach uses EPIDYS and OLE study data for givinostat and UK real-world data for ECM.[178] These data are considered most relevant to the decision problem. Relative efficacy is estimated for age at loss of ambulation, age at non-invasive ventilation, and age at FVC<1L |
| Source of patient utilities | Landfeldt et al. 2020; (Delphi panel)[197] | Project HERCULES UK BOI study and | Audhya et al. 2023[95] | Audhya et al. 2023 is the main study informing the patient HRQoL due to its alignment with the health states in the CEM, |


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| | | | | |
|---|---|---|---|---|
| | | Landfeldt et al. 2014; 2016a[49, 56] | | it collected patient-reported outcomes, and the measure used was the EQ-5D-5L – aligning with the NICE preference for a generic instrument. Alternative patient HRQoL sources are explored in scenario analyses |
| Source of caregiver utilities | Landfeldt et al. 2014; 2016b[45, 56] | Project HERCULES UK BOI study and Landfeldt et al. 2014; 2016b | UK caregiver vignette study[98] | The UK caregiver vignette study was commissioned by Pfizer. The study uses time-trade-off methodology to estimate the mean utility scores for eight DMD caregiver vignettes based on the health states as defined in the Project HERCULES NHM. This study is the main study informing the caregiver HRQoL due to its alignment with the health states in the CEM and its alignment with expected caregiver HRQoL across the progression of DMD. An alternative caregiver HRQoL source is explored in a scenario analysis |
| Source of costs | BNF and published literature for health state costs | BNF, NHS Reference Costs, PSSRU, Project HERCULES BOI study, published literature for health state costs, and NICE HST22 for spinal fusion surgery costs | eMIT, BNF, NHS Reference Costs, published literature for health state costs, and ongoing and previous NICE appraisals in DMD for spinal fusion surgery costs[7, 130, 194, 195, 204] | NICE reference case |

Abbreviations: BNF, British National Formulary; BOI, burden of illness; CEM, cost-effectiveness model; ECM, established clinical management; eMIT, electronic marketing information tool; EQ-5D-3L, EuroQol 5-dimensions 3-levels; FVC, forced vital capacity; HRQoL, health-related quality of life; HST, highly specialized technologies; MAIC, matched adjusted indirect comparison; NHM, natural history model; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal and Social Services; PSSRU, Personal Social Services Research Unit; UK, United Kingdom.


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### B.3.2.3 Intervention technology and comparators

**Givinostat**

In line with the final scope, the intervention in the CEM is givinostat.[198] The recommended dose of givinostat is based on body weight. Givinostat is administered orally twice daily with food.

In the CEM, the dose of givinostat reflects the EPIDYS clinical trial (Appendix M.2, Table 46). Table 42 below presents the number and proportion of patients receiving each of the weight-based dose distributions from the EPIDYS clinical trial; these data are weighted by the dose per day to calculate the average weight-based distribution which is applied in the CEM. The CEM accounts for treatment duration and variations in dose over time using the data from EPIDYS and the OLE – see Section B.3.3.4 and B.3.5.2, respectively.

**Table 42: Number of patients receiving each of the weight-based dose distributions in the EPIDYS clinical trial and calculation of average weight-based dose distribution**

| Weight | 10-12.5 Kg | 12.5-20 Kg | 20-25 Kg | 25-30 Kg | 30-40 Kg | 40-50 Kg | 50-60 Kg | 60-70 Kg | 70 Kg |
|---|---|---|---|---|---|---|---|---|---|
| Dose Regimen 1 starting dose, N (%) | 0 (0.0%) | 7 (70.0%) | 15 (79.0%) | 18 (58.1%) | 6 (15.0%) | 1 (6.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dose Regimen 1 permitted dose reduction, N (%) | 0 (100.0%) | 1 (10.0%) | 2 (10.5%) | 10 (32.3%) | 23 (57.5%) | 10 (66.7%) | 1 (100.0%) | 2 (100.0%) | 0 (100.0%) |
| Dose Regimen 2, N (%) | 0 (0.0%) | 2 (20.0%) | 2 (10.5%) | 3 (9.7%) | 11 (27.5%) | 4 (26.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Average dose per day (mg) | 26.6 | 43.7 | 55.0 | 59.3 | 54.5 | 65.3 | 73.4 | 80.0 | 93.4 |

Abbreviations: kg, kilogram; mg, milligram; N, number

Givinostat is given in addition to ECM. Feedback from the clinicians attending the medical and the HTA advisory boards conducted by ITF in 2024 indicated that givinostat has a different additive mechanism of action from ECM and, because of this, givinostat would be given in addition to current practice.[19, 20] Therefore, givinostat is not expected to impact ECM and this is modelled as per the ECM arm.

**Established clinical management**

In line with the NICE final scope, the relevant comparator is ECM without givinostat. Despite not being indicated for the treatment of DMD in the UK, oral CS, including prednisone or deflazacort, are the ECM for DMD, as per the International DMD Care Considerations guidelines and UK clinical feedback from clinicians attending the June 2024 HTA advisory board.[11, 20, 43, 124] Oral CS reduce inflammation, slow the progression of muscle weakness, reduce the development of scoliosis, and delay respiratory and cardiovascular problems.

As per the BNF guidelines, prednisone is administered orally as 0.75 mg/kg daily and deflazacort is administered orally as 0.90 mg/kg daily.[194] In clinical practice, CS may be given based on a daily dosing or an intermittent dosing schedule. In EPIDYS (N=179), 147


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(82.1%) patients received a daily schedule; 32 (17.9%) patients received an intermittent schedule reflecting every other day (2.8%), 10-days on and 5-days off (1.1%), 10-days on and 10-days off (10.1%), and only during the weekend (3.9%).[22, 132, 136] These data align with feedback from UK clinicians, who indicated that following the outcomes reported in Guglieri et al. 2022 - where daily dosing regimens were shown to have significant improvements compared with intermittent dosing regimens - most patients with DMD in UK clinical practice will receive daily dosing schedules.[19, 20, 205] The EPIDYS data are also supported by a real-world retrospective analysis of the UK NorthStar database, based on data collected between 2006 and 2020.[206] In the NorthStar data, of the N=576 receiving CS, 366 (63.5%) patients received a daily schedule and 210 (36.5%) received an intermittent schedule. The study indicates that the most common approach to intermittent schedules in the UK is 10-days on and 10-days off. Therefore, as a simplifying assumption, it is assumed that patients receiving an intermittent schedule receive half the dose of those patients receiving a daily schedule. This is not anticipated to have a significant impact on cost-effectiveness results as ECM is received in both treatment arms.

In the base case, the distribution of CS and associated dosing schedules comprising ECM are informed by the EPIDYS data (Table 17); 35 (19.6%) patients received prednisone and 136 (76.0%) received deflazacort across both givinostat and placebo treatment arms. Eight patients received other steroids which were not reflective of UK clinical practice. Therefore, the CEM assumes 20.5% (35/[35+136]) and 79.5% (136/[35+136]) of patients receive prednisone and deflazacort, respectively. In terms of dosing schedule, as per EPIDYS, 82.1% are assumed to receive a daily schedule and 17.9% are assumed to receive an intermittent schedule reflecting 10-days on and 10-days off i.e., half the dose of those patients receiving the daily schedule.

A scenario analysis considers the distribution of CS and associated dosing schedules comprising ECM from the analysis of the UK NorthStar database; 75.2% (N=433) of patients were reported to receive prednisone, 24.8% (N=143) were reported to receive deflazacort, 63.5% received a daily schedule, and 36.5% received an intermittent schedule.

## *B.3.3 Clinical parameters and variables*

### B.3.3.1 Natural history model (NHM)

**Published NHM**

As described in Section B.3.2, one of the key outputs from the Project HERCULES initiative is the development of a CEM building on the published NHM as presented in Broomfield et al. 2024.[191] Section B.3.2.2 details the process for defining the health states underpinning the published NHM.

The primary data source informing the published NHM is the Critical Path Institute (C-Path) Duchenne Regulatory Science Consortium (D-RSC) database. D-RSC comprises patient level multinational clinical data for DMD. The dataset contains anonymised individual patient data (IPD) from 11 international data sources, including natural history studies, placebo arms of clinical trials, and registry data. In total, 4,467 transitions were observed across the health states.


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However, no data were available on the transition intensities to and from the "(3) transfer" health state; instead, this was informed by data from an elicitation exercise conducted by the University of Leicester. Additionally, limited data were available to inform the transition intensities to and from the "(4) HTMF, no ventilation", "(5) no HTMF, no ventilation", and "(6) HTMF, nighttime ventilation" health states. Therefore, these were augmented by data from the elicitation exercise.

The exercise included an initial pilot, in which information was elicited from four clinicians and four caregivers involved in the Project HERCULES collaboration, followed by an online survey of 20 UK stakeholders, including healthcare practitioners, parents, and caregivers. The anonymized online survey was circulated by Duchenne UK and received 20 responses all from the UK. In the survey, respondents were asked the average age at which patients enter and exit health states (Table 43). From the responses received, the mean age and standard deviation (SD) upon entry and exit to the health states were estimated and used to generate pseudo individual patient data (IPD) from which transition intensities could be estimated.

**Table 43: Questions used in the elicitation exercise**

| | |
|---|---|
| Question 1 | On average, at what age would you expect someone with DMD to stop being able to walk 10m (but still be able to stand, i.e. weight bearing)? [state 2 to state 3]<br>Can you specify a plausible range for this average? |
| Question 2 | Given what you have said about the average in Question 1, how long would you expect it to be before they lose the ability to stand? (or say, on average, at what age you think this would happen, if that is easier) [state 3 to state 4]<br>Can you specify a plausible range for this average? |
| Question 3 | Given what you have said in Questions 1 and 2, if someone has lost the ability to stand, but still has HTMF and does NOT require any ventilation:<br>On average, how long do you think it would be before they lost either HTMF or required nighttime ventilation? (or say, on average, at what age you think this would happen, if that is easier) [state 4 to state 5 or 6]<br>Can you specify a plausible range for this average?<br>What proportion (%) of patients do you think would lose HTMF first? [state 4 to state 5] |

Abbreviations: DMD, Duchenne muscular dystrophy; HTMF, hand to mouth function

As no mortality data were available from the D-RSC dataset, an SLR and meta-analysis were performed to identify published mortality data in DMD – this has been published in Broomfield et al. 2020. Kaplan Meier curves from 14 studies were digitised and IPD reconstructed. The digitised mortality data contained 2,283 patients and 1,050 deaths across the 14 studies. Mortality rates were determined from a parametric survival model assuming a piecewise constant hazard function using an increased rate of mortality after age 30-years in the full-time ventilation states.

The published NHM assumed that DMD is progressive i.e. no backwards transitions were permitted – as supported by the C-Path D-RSC data and validated by UK clinicians. Transition intensities were then estimated via the following six steps:

(1) the mean age of patients observed in each state in the D-RSC dataset was estimated.


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(2) To estimate the mortality rate for each state, a piecewise constant hazard function was fitted to the mortality data, with cut points determined by the mean age in each state.

(3) The initial values of a transition intensity matrix were specified using the estimated mortality rates and setting transition intensities for all transient states to 0.1 (initial transition intensities of 0.01 and 1 were also considered).

(4) A multistate model was fitted in R using the msm package using the specified transition intensity matrix and fixing mortality rates at their initial values.

(5) A new transition intensity matrix was then defined using the transition intensities estimated in Step 4 and mortality rates estimated in Step 2.

(6) Steps 4 and 5 were then repeated using the newly defined transition intensity matrix until the model converged. Convergence was defined as transition intensities being equal to 4 decimal places. The model converged after two iterations.

An exponential distribution (i.e. constant transition intensities) was used to fit the multistate model for transitions up to health states defined by the requirement for full-time ventilation. A piecewise exponential distribution was assumed for transitions from full-time ventilation states to death. The published NHM assumes that the mortality rate varies only by health state.

Transition intensities from the published NHM were converted into transition probabilities to determine health state membership over time for ECM. The probability of transitioning from state $i$ to state $j$ is calculated according to the formula:

$$p_{i.j} = \frac{q_{i.j}(1 - \exp\left(-\sum_{r \neq i} q_{i,r}\right))}{\sum_{r \neq i} q_{i,r}}$$

Where $p_{i.j}$ is the probability of transitioning from state $i$ to state $j$ and $q_{i.j}$ is the transition intensity transitioning from state $i$ to state $j$. This approach of estimating transition probabilities from the transition intensities does not allow patients to skip health states. Therefore, it is assumed that patients can only move to the adjacent health state or death – this is supported by the granular cycle length (one month) and reduces the computational complexity in the Microsoft Excel-based model. Additionally, it is aligned with the approach in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135).[130] Appendix M.7.1 presents the transition probabilities estimated by the published NHM, split by patients under and over the age of 30, respectively.

There are many advantages of the published NHM. It provides a set of transition intensities to inform the natural history of DMD in economic evaluations of new treatments, where previously there has been a paucity of data to inform health state transitions over the lifetime of patients. Additionally, the published NHM has been developed with input from patients, caregivers, and clinicians, which means that the health states reflect clinically important changes in patient care and HRQoL.

However, there are limitations associated with the steps taken to overcome the paucity of data in the published NHM – as discussed in Broomfield et al. 2024. Notably, sparse data

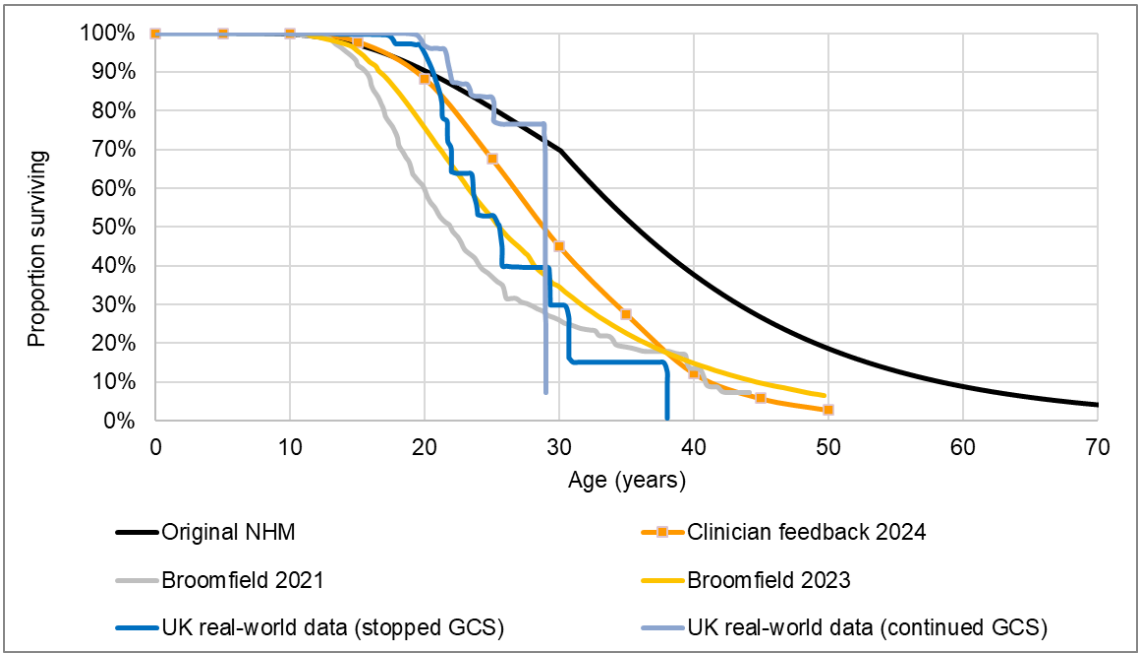

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meant that the exponential distribution was used to fit the multi-state model, initially across all health states. However, its use resulted in clinically implausible mean durations in health states (8a) and (8b). Therefore, a piecewise exponential was assumed for transitions out of these health states to death, which was found to partly address this issue. However, the mean ages in health states (8a) and (8b) predicted by the published NHM are still higher than expected given the C-PATH D-RSC data – as reported in the publication.

The over-estimation of survival aligns with the feedback in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135), where the clinical experts and the committee noted that the median survival expected for patients with DMD from the literature was less than predicted by the published NHM. The committee concluded in the draft guidance that the published NHM may have overestimated life expectancy for DMD.

Figure 35 and Table 44 compare the survival over time predicted by the published NHM with a meta-analysis of published survival data reported in Broomfield et al. 2021, survival estimates from the UK CPRD cohort study reported in Broomfield et al. 2023, survival estimates from unpublished data reflecting outcomes for N=156 patients treated with CS across center's in London, Newcastle, and Oxford (UK real-world data), and landmark estimates predicted by six clinicians at the April 2024 medical advisory board.[19, 37, 38, 178, 191] The predicted survival from the published NHM is shown to be higher than all alternative sources. Importantly, all external data sources indicate similar survival over time.

**Figure 35: A comparison of survival from the published NHM with the literature, UK real-world data, and clinician feedback[37, 38, 178, 191]**




Abbreviations: GCS, glucocorticosteroids; NHM, natural history model.


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**Table 44: A comparison of survival from the published NHM with the literature, UK real-world data, and clinician feedback**

| | Published NHM[191] | Broomfield 2021[38] | Broomfield 2023[37] | Clinical feedback 2024[19] | UK real-world data (stopped GCS)[178] | UK real-world data (continued GCS) | Weighted UK real-world data |
|---|---|---|---|---|---|---|---|
| Median | 35.58 | 21.83 | 25.37 | NA | 25.50 | 28.95 | 27.85 |
| **% surviving at (age):** | | | | | | | |
| 10 | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| 20 | 90% | 61% | 76% | 88% | 97% | 97% | 97% |
| 30 | 70% | 26% | 35% | 45% | 30% | 7%** | 15% |
| 40 | 38% | 14% | 15% | 12% | 1%* | NA | 5% |
| 50 | 19% | 7% | 6% | 3% | NA | NA | NA |

Abbreviations: GCS, glucocorticosteroids; NA, not available; NHM, natural history model
*% surviving based on last available data point at age 38. **% surviving based on last available data point at age 29.

### Updated NHM

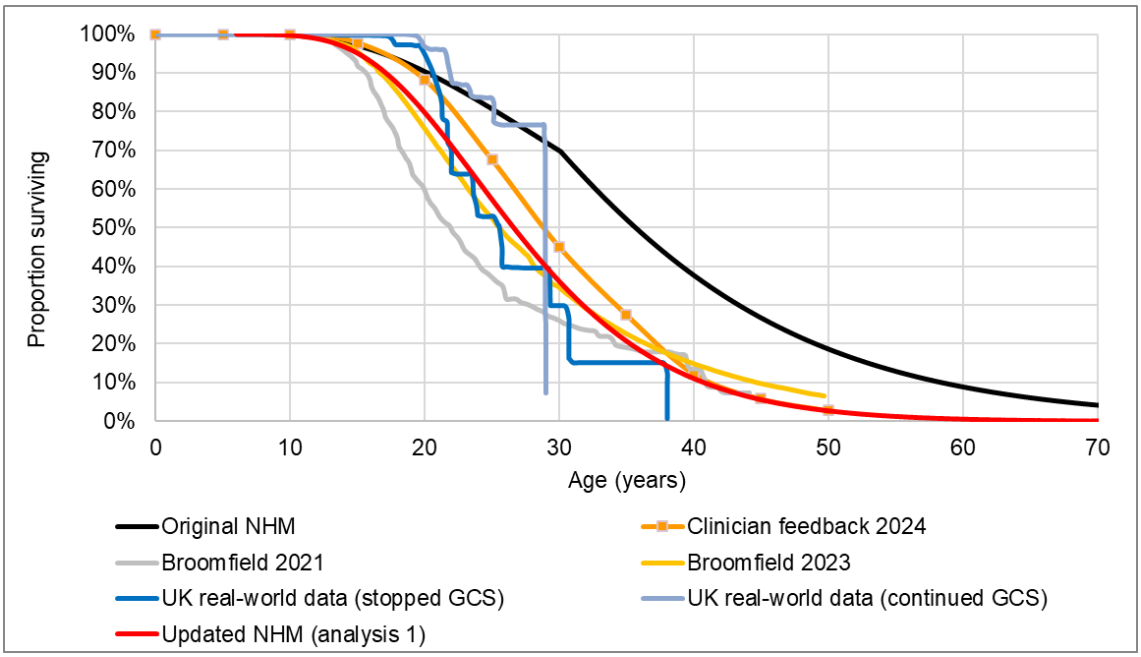
Two approaches have been explored to align long-term outcomes from the published NHM with external UK data sources.

As the piecewise exponential approach for mortality using a 30-year timepoint was employed by the authors of the published NHM to attempt to align long-term survival with clinical expectations, this has been removed when exploring alternative approaches. Therefore, the transition probabilities estimated by the published NHM for patients aged <30-years are explored alongside the external real-world data. The CEM includes the option to include the piecewise exponential approach. However, this creates an artificial kink in the extrapolated survival which is not considered clinically plausible and is considered superfluous in these analyses.

In line with the discussion in Broomfield et al. 2024 surrounding the over-estimation in survival stemming from the final health states. The first analysis (updated NHM [analysis 1]) estimated the hazard ratio (HR) that would be required and applied to the transitions from health states (8a) and (8b) to death to align the NHM outcomes with the proportion of patients predicted to be alive at 50-years based on UK clinical expert feedback collected in the medical advisory board in April 2024 (i.e., 2.8%). This approach used the SOLVER functionality in Microsoft Excel to estimate the HR required to ensure the proportion surviving at 50-years aligned with 2.8%. This returned a HR of 8.3 for transitions from health states (8a) and (8b) to death. Figure 36 compares the predicted survival estimated from the updated NHM (analysis 1) with the external sources. The updated NHM (analysis 1) is shown to closely align with published and unpublished survival data, as well as with the UK clinician feedback (Table 45).


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**Figure 36: A comparison of survival from the updated NHM (analysis 1) with external sources and the published NHM[37, 38, 178, 191]**




Abbreviations: FVC, forced vital capacity; GCS, glucocorticosteroids; NHM, natural history model.

**Table 45: A comparison of survival from the updated NHM (analysis 1) with external sources and the published NHM**

| | Updated NHM (analysis 1) | Published NHM[191] | Broom-field 2021[38] | Broom-field 2023[37] | Clinical feedback 2024[19] | UK real-world data (stopped GCS)[178] | UK real-world data (continued GCS) | Weighted UK real-world data |
|---|---|---|---|---|---|---|---|---|
| Median | 26.6 | 35.6 | 21.8 | 25.4 | NA | 25.5 | 28.9 | 27.8 |
| **% surviving at (age):** | | | | | | | | |
| 10 | 99.7% | 99.7% | 99.9% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| 20 | 79.7% | 90.3% | 60.7% | 76.1% | 88.2% | 97.0% | 97.0% | 97.0% |
| 30 | 36.1% | 69.9% | 26.0% | 34.6% | 45.0% | 29.8% | 7.3%** | 14.5% |
| 40 | 11.2% | 37.8% | 13.6% | 15.3% | 12.3% | 0.6%* | NA | 0.6% |
| 50 | 2.8% | 18.7% | 7.3% | 6.4% | 2.8% | NA | NA | NA |

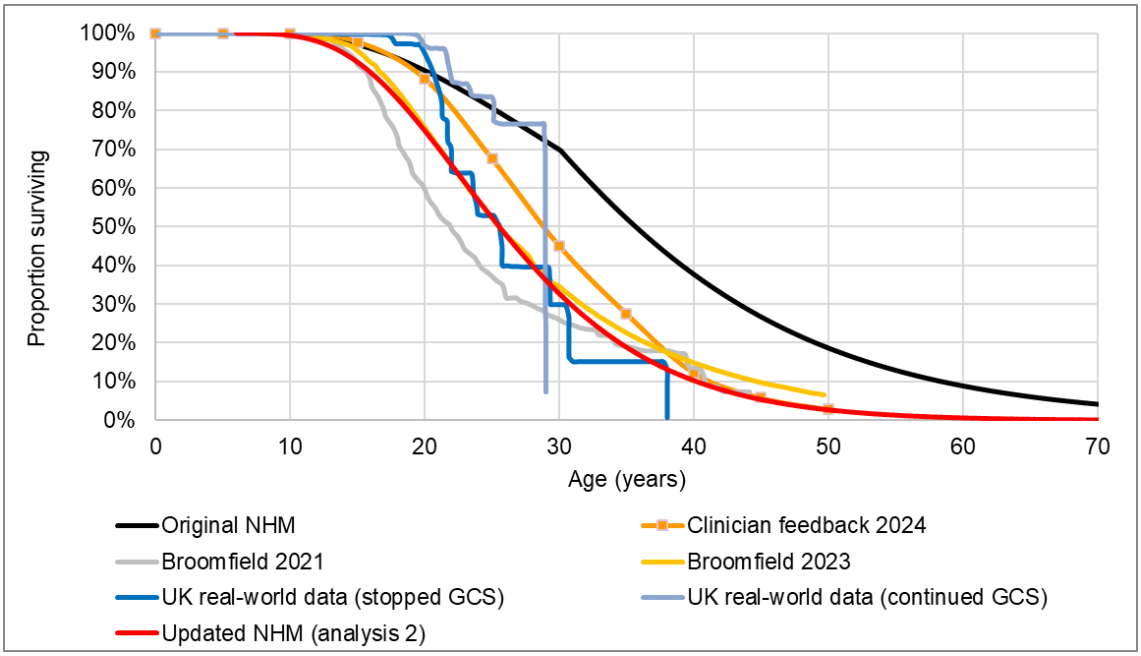
Abbreviations: GCS, glucocorticosteroids; NHM, natural history model
*% surviving based on last available data point at age 38. **% surviving based on last available data point at age 29.

The second analysis (updated NHM [analysis 2]) explored the potential for over-estimated transition probabilities in the published NHM earlier in the disease pathway. The published NHM estimates that the median age of loss of ambulation is 15.5 years. The unpublished UK-real world data suggests that, in clinical practice, patients may lose their ambulation earlier with a median age at loss of ambulation of 12.1 years. Therefore, the second analysis (updated NHM [analysis 2]) estimated two sets of HRs using the SOLVER functionality: first


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the HR applied to transitions from health states (1) to (2), (2) to (3), and (3) to (4) and second the HR applied to transitions from health states (8a) and (8b) to death to align the median age at loss of ambulation with the unpublished UK real-world data and to ensure the proportion surviving at 50-years aligned with 2.8%. This returned a HR of 1.6 for transitions from (1) to (2), (2) to (3), and (3) to (4) and 3.8 for transitions from health states (8a) and (8b) to death. Figure 37 compares the predicted survival estimated from the updated NHM (analysis 2) with the external sources and the published NHM. The updated NHM (analysis 2) is shown to closely align with published and unpublished survival data, as well as with the UK clinician feedback (Table 46).

**Figure 37: A comparison of survival from the updated NHM (analysis 2) with external sources and the published NHM[37, 38, 178, 191]**




Abbreviations: GCS, glucocorticosteroids; NHM, natural history model.


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**Table 46: A comparison of survival from the updated NHM (analysis 2) with external sources and the published NHM**

| | Updated NHM (analysis 2) | Published NHM[191] | Broom-field 2021[38] | Broom-field 2023[37] | Clinical feedback 2024[19] | UK real-world data (stopped GCS)[178] | UK real-world data (continued GCS) | Weighted UK real-world data |
|---|---|---|---|---|---|---|---|---|
| Median | 25.5 | 35.6 | 21.8 | 25.4 | NA | 25.5 | 28.9 | 27.8 |
| **% surviving at (age):** | | | | | | | | |
| 10 | 99.4% | 99.7% | 99.9% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| 20 | 74.8% | 90.3% | 60.7% | 76.1% | 88.2% | 97.0% | 97.0% | 97.0% |
| 30 | 32.7% | 69.9% | 26.0% | 34.6% | 45.0% | 29.8% | 7.3%** | 14.5% |
| 40 | 10.4% | 37.8% | 13.6% | 15.3% | 12.3% | 0.6%* | NA | 0.6% |
| 50 | 2.8% | 18.7% | 7.3% | 6.4% | 2.8% | NA | NA | NA |

Abbreviations: GCS, glucocorticosteroids; NA, not available; NHM, natural history model
*% surviving based on last available data point at age 38. **% surviving based on last available data point at age 29.

In the base case, the updated NHM (analysis 2) is applied. There are limited differences across survival predictions from updated NHM (analysis 1) and updated NHM (analysis 2). However, the predicted median age at loss of ambulation, starting nighttime ventilation, and starting fulltime ventilation are more closely aligned with the UK real-world data when using the updated NHM (analysis 2) – see Table 47. Therefore, the updated NHM (analysis 2) is the most externally valid option to inform the base case. A scenario analysis explores the impact of the updated NHM (analysis 1) and the published NHM with the piecewise exponential approach. This approach to adjusting the published NHM has been validated with experts involved in the development of the Project HERCULES CEM.

**Table 47: Comparison of age milestones from published NHM, updated NHMs, and UK real-world data**

| Median age at: (in years) | Updated NHM (analysis 1) | Updated NHM (analysis 2) | UK real-world data[178] | Published NHM[191] |
|---|---|---|---|---|
| Unable to stand from supine | 10.2 | 8.7 | NA | 10.2 |
| Loss of ambulation | 15.5 | 12.1 | 12.1 | 15.5 |
| Starting ventilation | 19.6 | 16.0 | 18.1 | 19.6 |
| Starting full time ventilation | 23.9 | 20.3 | 20.5 | 23.9 |
| Death | 26.6 | 25.5 | 28.0 | 35.6 |

Abbreviations: NA, not available; NHM, natural history model.

Table 48 presents the transition probabilities estimated by the updated NHM (analysis 2) following the adjustments described above – these are applied for ECM in the CEM.


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**Table 48: Transition probabilities from the updated NHM (analysis 2)**

| From/To | State 1 | State 2 | State 3 | State 4 | State 5 | State 7A | State 8A | State 6 | State 7B | State 8B | State 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| State 1 | 97.9% | 2.1% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| State 2 | 0.0% | 96.3% | 3.7% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| State 3 | 0.0% | 0.0% | 91.9% | 8.1% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| State 4 | 0.0% | 0.0% | 0.0% | 95.3% | 2.4% | 0.0% | 0.0% | 2.3% | 0.0% | 0.0% | 0.1% |
| State 5 | 0.0% | 0.0% | 0.0% | 0.0% | 98.3% | 1.6% | 0.0% | 0.0% | 0.0% | 0.0% | 0.1% |
| State 7A | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 96.5% | 3.3% | 0.0% | 0.0% | 0.0% | 0.3% |
| State 8A | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 98.8% | 0.0% | 0.0% | 0.0% | 1.2% |
| State 6 | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 98.2% | 1.5% | 0.0% | 0.2% |
| State 7B | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 95.6% | 4.1% | 0.3% |
| State 8B | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 98.8% | 1.2% |
| State 9 | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 100.0% |


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As an additional check for clinical plausibility, the per cycle rate of death is compared to the mortality rate in the general population matched for gender and age in each cycle in the CEM, using National life tables for England and Wales 2020-2022 from the ONS.[207] If the matched general population rate is higher, this is used in the CEM for that cycle. Note: background mortality only impacts transitions to death from health state (1).

#### *B.3.3.2* Comparative efficacy of givinostat

The relative efficacy of givinostat vs. ECM has been estimated through unanchored MAICs (Section B.2.8) using data from the EPIDYS and OLE studies (N=148) for givinostat matched to align with UK real-world data for ECM.

The unanchored MAICs are based on outcomes measured from baseline. However, the CEM applies HRs to transitions between the health states. For example, the probability of losing ambulation in the CEM is based on a combination of the probability of progressing from health state (1) to (2), the probability of progressing from health state (2) to (3), and the probability of progressing from health state (3) to (4), as well as the probability of death from any of these ambulatory health states. Therefore, the CEM uses the data estimated by the MAICs and applies necessary assumptions to fit these outcomes to the granularity of the CEM.

The unanchored MAIC analyses predict:

- A HR of 0.185 (95% CI: 0.121 – 0.282) for age at loss of ambulation for givinostat vs. ECM. The median for the unadjusted givinostat data is 17.97 (95% CI: 15.40 – NE) and for the MAIC-weighted givinostat data is NE (95% CI: 15.52 – NE).
- A HR of 0.190 (95% CI: 0.124 – 0.290) for age at non-invasive ventilation for givinostat vs. ECM. The median for the unadjusted givinostat data is 27.00 (95% CI: 23.14 - NE) and for the MAIC-weighted givinostat data is NE (95% CI: 23.32 – NE).
- A HR of 0.214 (95% CI: 0.139 – 0.329) for age at FVC<1L for givinostat vs. ECM. The median for the unadjusted givinostat data is 34.90 (95% CI: 29.91 - NE) and for the MAIC-weighted givinostat data is NE (95% CI: 30.14 – NE).

As described above, owing to the multiple transitions modelled within each endpoint, the HRs estimated by the MAICs cannot be applied directly within the CEM structure. Therefore, independent parametric curves were fit to the MAIC-weighted givinostat data to estimate median values for age at loss of ambulation, age at non-invasive ventilation, and age at FVC<1L. Note: median values were not estimable from the MAIC-weighted givinostat Kaplan-Meier data. The CEM then used SOLVER to estimate the HRs relevant to transitions from:

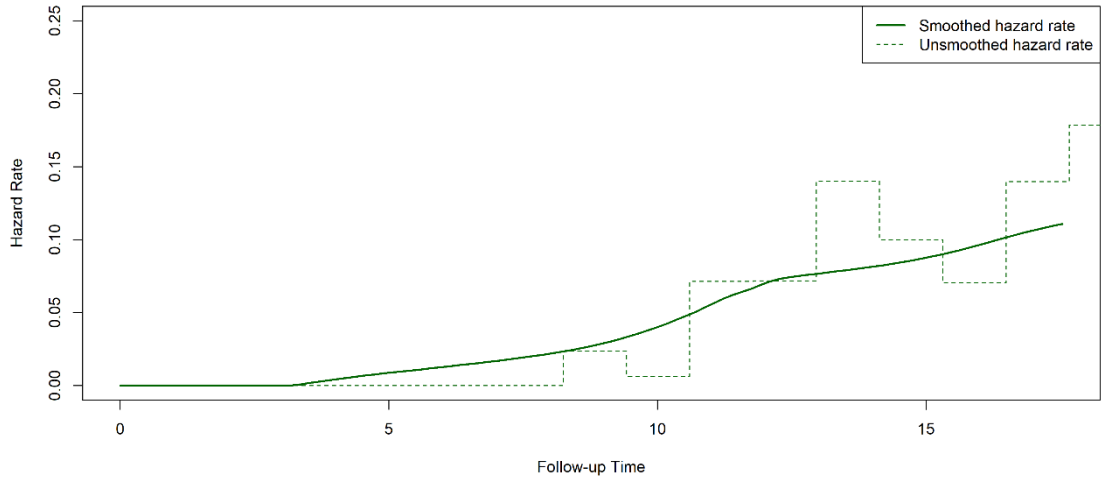
- Health states (1) to (2), (2) to (3), and (3) to (4), such that the predicted median age at loss of ambulation from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat loss of ambulation data.
- Health states (4) to (5), (4) to (6), and (5) to (7a), such that the predicted median age at ventilation from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat non-invasive ventilation data.


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- Health states (6) to (7b), (7a) to (8a), and (7b) to (8b), such that the predicted median age at FVC<30% from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat FVC<1L data. As per the clinical advice provided to the EAG in the NICE submission for ataluren, it is considered reasonable to assume that FVC<1L is equivalent to FVC<30% i.e. aligning with health states (8a) and (8b) in the CEM.[7]

Figure 31, Figure 32, and Figure 33 in Section B.2.8.4 present the MAIC-weighted givinostat data for loss of ambulation, non-invasive ventilation, and FVC<1L outcomes, respectively. Figure 38, Figure 39, and Figure 40 present the hazards underpinning the MAIC-weighted Kaplan-Meier plots. Note: due to the assumptions required in the MAICs, the hazard profile is the same shape for all outcomes – see Section B.2.8.4. As would be expected with the progression profile of DMD, the hazards of an event are shown to steadily increase over time.

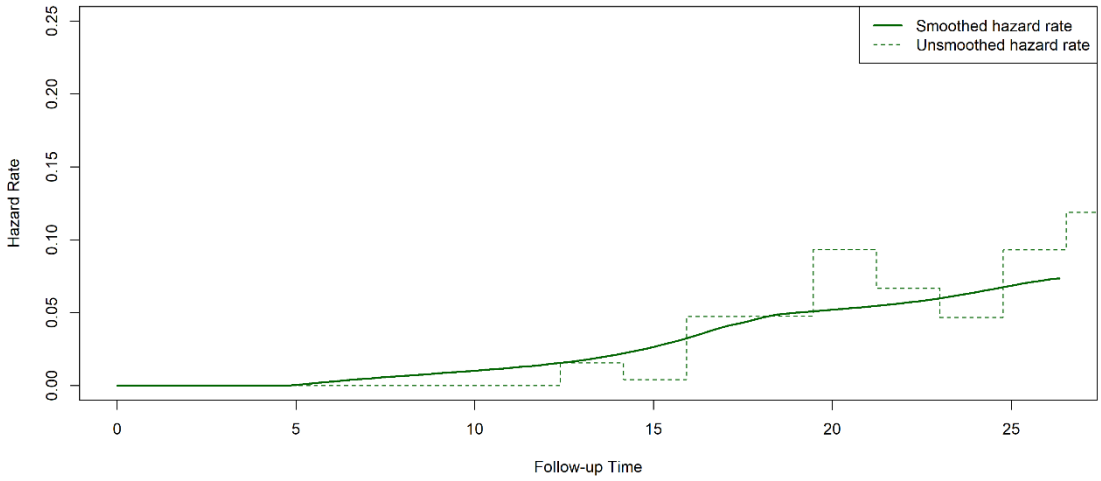
**Figure 38: Hazards corresponding to the MAIC-weighted Kaplan-Meier data for age at loss of ambulation (Section B.2.8.4, Figure 31)**




Abbreviations: MAIC, matched adjusted indirect comparison.

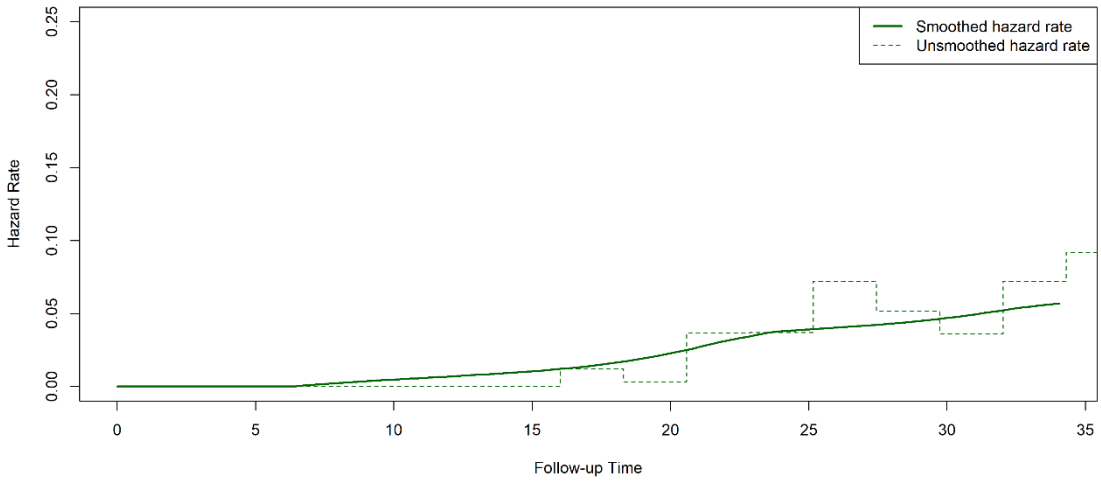

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**Figure 39: Hazards corresponding to the MAIC-weighted Kaplan-Meier data for age at non-invasive ventilation (Section B.2.8.4, Figure 32)**




Abbreviations: MAIC, matched adjusted indirect comparison.

**Figure 40: Hazards corresponding to the MAIC-weighted Kaplan-Meier data for age at FVC<1L (Section B.2.8.4, Figure 33)**

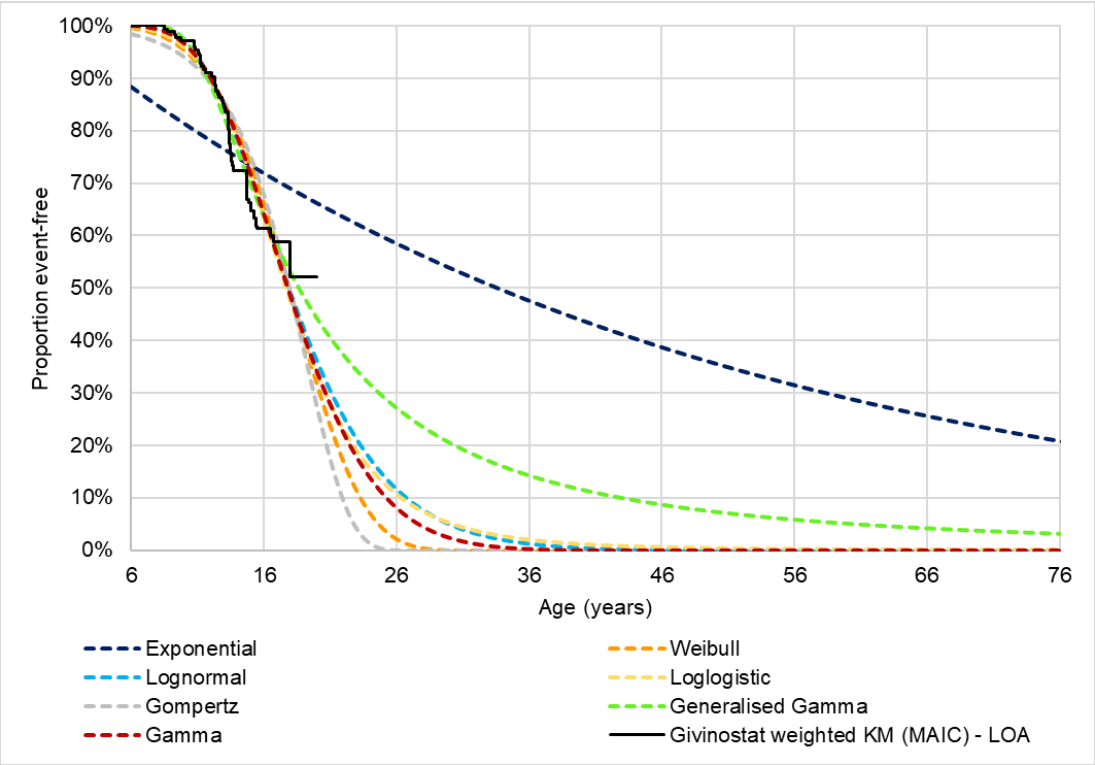



Abbreviations: FVC, forced vital capacity; MAIC, matched adjusted indirect comparison.

Independent parametric curves were fit to the MAIC-weighted Kaplan-Meier data in accordance with the NICE DSU 14; the exponential, Weibull, Gompertz, log-normal, log-logistic, generalized gamma, and gamma standard parametric curves were fit to these data.[208] Figure 41, Figure 42, and Figure 43 present the extrapolated independent parametric curves fitted to the MAIC-weighted givinostat data for loss of ambulation, non-invasive ventilation, and FVC<1L outcomes, respectively. The corresponding AIC and BIC values are presented in Table 49. Table 50 presents the predicted median age at loss of ambulation, non-invasive ventilation, and FVC<1L across all parametric curves.

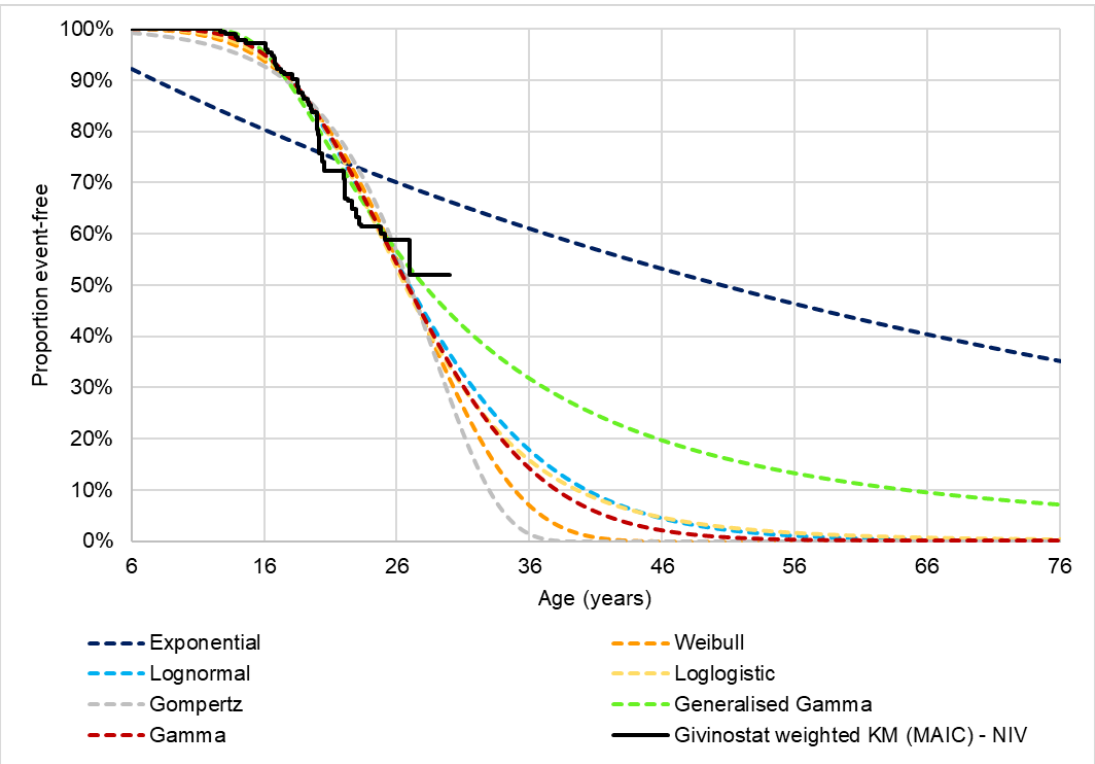

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**Figure 41: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at loss of ambulation**




Abbreviations: KM, Kaplan-Meier; LOA, loss of ambulation; MAIC, matched adjusted indirect comparison.

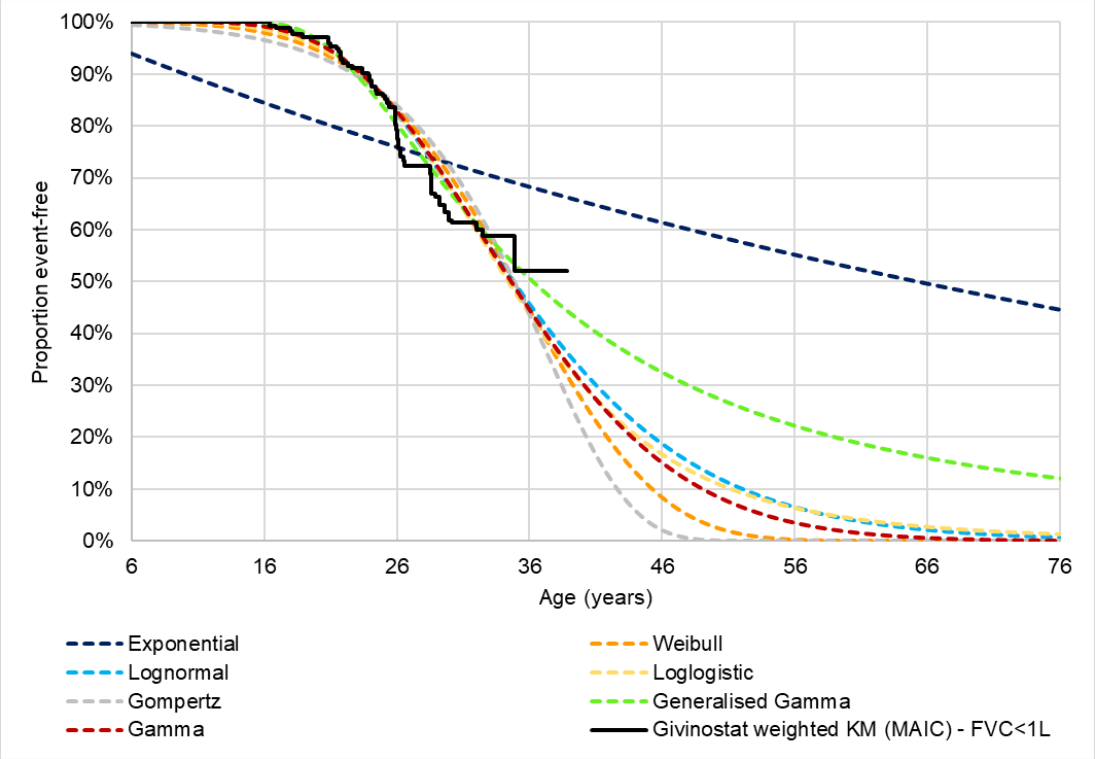
**Figure 42: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at non-invasive ventilation**




Abbreviations: KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison; NIV, non-invasive ventilation.


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**Figure 43: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at FVC<1L**




Abbreviations: FVC, forced vital capacity; KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison.

**Table 49: AIC and BIC values corresponding to independent parametric curves fit to the MAIC-weighted Kaplan-Meier data for givinostat**

| | AIC | BIC | Rank (AIC) | Rank (BIC) |
|---|---|---|---|---|
| **Loss of ambulation** | | | | |
| **Exponential** | 356 | 359 | 7 | 7 |
| **Weibull** | 290 | 296 | 5 | 5 |
| **Lognormal** | 283 | 289 | 2 | 1 |
| **Loglogistic** | 286 | 292 | 4 | 4 |
| **Gompertz** | 299 | 305 | 6 | 6 |
| **Generalised Gamma** | 282 | 291 | 1 | 3 |
| **Gamma** | 285 | 291 | 3 | 2 |
| **Non-invasive ventilation** | | | | |
| **Exponential** | 386 | 389 | 7 | 7 |
| **Weibull** | 320 | 326 | 5 | 5 |
| **Lognormal** | 312 | 318 | 2 | 1 |
| **Loglogistic** | 316 | 322 | 4 | 4 |
| **Gompertz** | 328 | 334 | 6 | 6 |
| **Generalised Gamma** | 311 | 320 | 1 | 3 |
| **Gamma** | 314 | 320 | 3 | 2 |
| **FVC<1L** | | | | |
| **Exponential** | 405 | 408 | 7 | 7 |
| **Weibull** | 338 | 344 | 5 | 5 |


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| | AIC | BIC | Rank (AIC) | Rank (BIC) |
|---|---|---|---|---|
| **Lognormal** | 331 | 337 | 2 | 1 |
| **Loglogistic** | 334 | 340 | 4 | 4 |
| **Gompertz** | 347 | 353 | 6 | 6 |
| **Generalised Gamma** | 330 | 339 | 1 | 3 |
| **Gamma** | 333 | 339 | 3 | 2 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; FVC, forced vital capacity; MAIC, matched adjusted indirect comparison.

**Table 50: Median values corresponding to independent parametric curves fit to the MAIC-weighted Kaplan-Meier data for givinostat**

| | Median | Lower bound | Upper bound |
|---|---|---|---|
| **Loss of ambulation** | | | |
| **Exponential** | 33.6 | 24.5 | 47.1 |
| **Weibull** | 17.9 | 16.5 | 19.2 |
| **Lognormal** | 17.9 | 16.8 | 19.2 |
| **Loglogistic** | 17.9 | 16.2 | 19.6 |
| **Gompertz** | 17.7 | 16.2 | 19.4 |
| **Generalised Gamma** | 18.6 | 16.6 | 23.1 |
| **Gamma** | 17.8 | 16.3 | 19.5 |
| **Non-invasive ventilation** | | | |
| **Exponential** | 50.5 | 37.0 | 70.7 |
| **Weibull** | 26.9 | 24.8 | 29.0 |
| **Lognormal** | 26.9 | 25.3 | 28.8 |
| **Loglogistic** | 26.9 | 24.6 | 29.7 |
| **Gompertz** | 26.6 | 24.3 | 29.0 |
| **Generalised Gamma** | 28.0 | 25.2 | 35.8 |
| **Gamma** | 26.8 | 24.5 | 29.1 |
| **FVC<1L** | | | |
| **Exponential** | 65.3 | 46.5 | 90.8 |
| **Weibull** | 34.8 | 32.3 | 37.5 |
| **Lognormal** | 34.8 | 32.4 | 37.6 |
| **Loglogistic** | 34.8 | 31.7 | 38.2 |
| **Gompertz** | 34.4 | 31.6 | 37.6 |
| **Generalised Gamma** | 36.2 | 31.9 | 45.3 |
| **Gamma** | 34.6 | 31.9 | 37.9 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; FVC, forced vital capacity; MAIC, matched adjusted indirect comparison.

The AIC and BIC indicate that the log-normal, generalized gamma, and gamma parametric curves provide the best fit to the loss of ambulation, non-invasive ventilation, and FVC<1L MAIC-weighted givinostat data – with a difference less than three across AIC and BIC scores. Note: due to the assumptions required in the MAICs, the rankings of AIC and BIC scores are the same for all outcomes – see Section B.2.8.4. Aligned with the lowest AIC and BIC scores, the medians predicted from the log-normal parametric curve are used in the SOLVER calculations when estimating the HRs relevant to transitions underpinning the model structure. This results in a HR of 0.51 being applied for transitions from health states


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(1) to (2), (2) to (3), and (3) to (4), a HR of 0.39 being applied for transitions from health states (4) to (5), (4) to (6), and (5) to (7a), and a HR of 0.46 being applied for transitions from health states (6) to (7b), (7a) to (8a), and (7b) to (8b).

Table 51 presents the HRs informing the individual health state transitions used in the CEM. These HRs are applied to the transition probabilities estimated through the updated NHM (analysis 2, see Section B.3.3.1) to inform the efficacy for givinostat in the CEM. As givinostat is not anticipated to directly impact the probability of dying, HRs of one are applied to all transitions to death.

Predicted median milestones are compared to those from the observed data and the fitted parametric curves in Table 52. The predicted event-free proportions for loss of ambulation, age at non-invasive ventilation, and age at FVC<30% by the CEM over the model time horizon are compared to the log-normal, generalized gamma, and gamma parametric curves fit to the MAIC-weighted givinostat data i.e., the best fitting parametric curves in Figure 44, Figure 45, and Figure 46, respectively. The predicted outcomes from the CEM are shown to align across the observed data and best fitting parametric curves, highlighting the validity of the CEM predictions.

**Table 51: HRs applied to health state transitions in the CEM**

| **Health state transitions** | **HR** |
|---|---|
| To state 2 - Late ambulatory | 0.51 |
| To state 3 - Transfer | 0.51 |
| To state 4 - HTMF, no ventilation | 0.51 |
| To state 5 - No HTMF, no ventilation | 0.39 |
| To state 7a - No HTMF, night-time ventilation | 0.39 |
| To state 8a - Full time ventilation | 0.46 |
| To state 6 - HTMF, night-time ventilation | 0.39 |
| To state 7b - No HTMF, night-time ventilation | 0.46 |
| To state 8b - Full time ventilation | 0.46 |
| **Mortality transitions** | **HR** |
| From state 1 - Early ambulatory | 1.00 |
| From state 2 - Late ambulatory | 1.00 |
| From state 3 - Transfer | 1.00 |
| From state 4 - HTMF, no ventilation | 1.00 |
| From state 5 - No HTMF, no ventilation | 1.00 |
| From state 7a - No HTMF, night-time ventilation | 1.00 |
| From state 8a - Full time ventilation | 1.00 |
| From state 6 - HTMF, night-time ventilation | 1.00 |
| From state 7b - No HTMF, night-time ventilation | 1.00 |
| From state 8b - Full time ventilation | 1.00 |

Abbreviations: CEM, cost-effectiveness model; HR, hazard ratio; HTMF, hand-to-mouth function.


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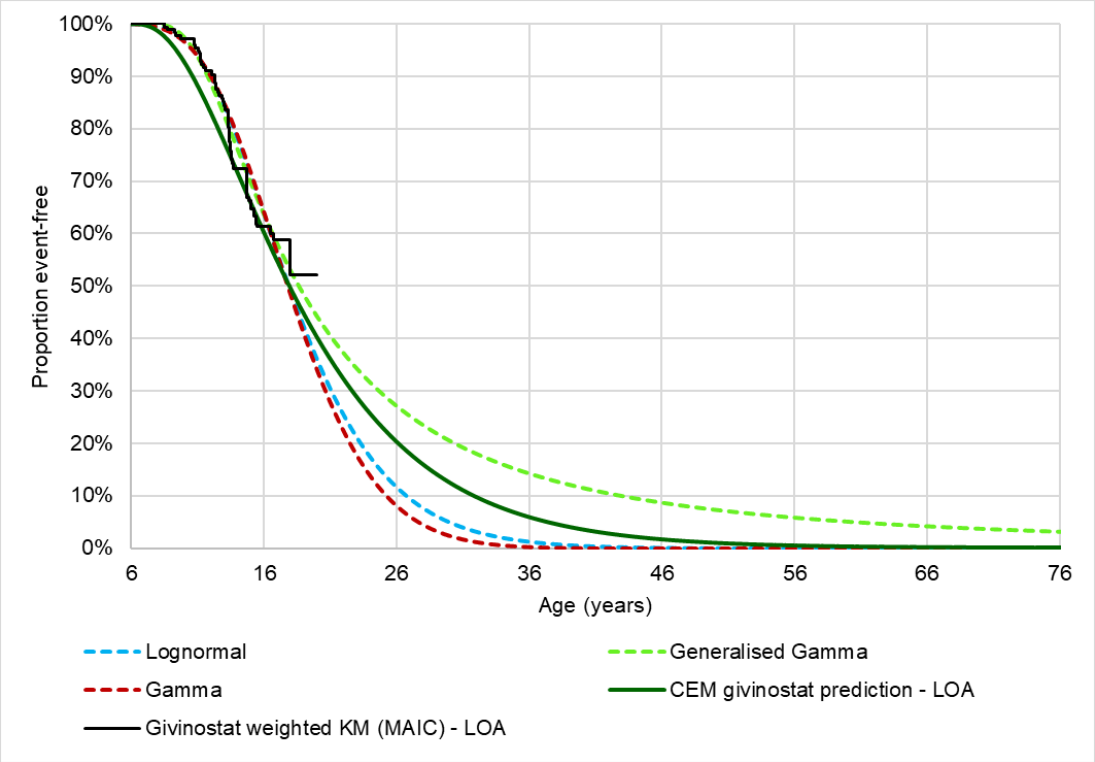
**Table 52: Median age at disease milestones**

| | Model predictions | | MAIC Kaplan-Meier data | | Parametric curves fit to MAIC-weighted givinostat data | | |
|---|---|---|---|---|---|---|---|
| **Median age at:** | **ECM** | **Givinostat** | **ECM** | **Givinostat** | **Log-normal** | **Generalised gamma** | **Gamma** |
| Unable to stand from supine | 8.67 | 11.25 | NA | NA | NA | NA | NA |
| Loss of ambulation | 12.08 | 17.92 | 12.28 | Weighted = NE<br>Unadjusted = 17.97 | 17.90 | 18.64 | 17.81 |
| Loss of HTMF | 15.92 | 26.00 | NA | NA | NA | NA | NA |
| Starting ventilation | 16.00 | 26.92 | 18.46 | Weighted = NE<br>Unadjusted = 27.00 | 26.89 | 28.01 | 26.76 |
| Starting full-time ventilation | 20.33 | 34.75 | 23.86 | Weighted = NE<br>Unadjusted = 34.90 | 34.76 | 36.21 | 34.60 |
| Death | 25.42 | 39.25 | NA | NA | NA | NA | NA |

Abbreviations: CEM, cost-effectiveness model; ECM, established clinical management; HR, hazard ratio; HTMF, hand-to-mouth function; MAIC, matched adjusted indirect comparison; NA, not available.

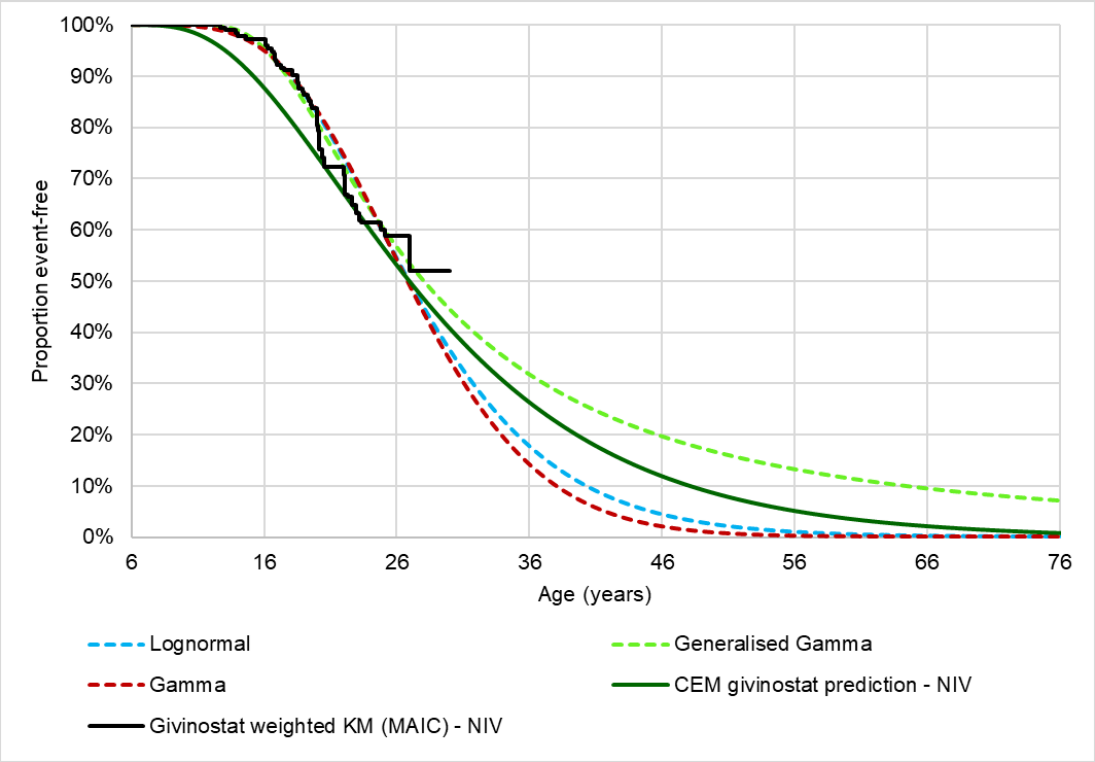

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**Figure 44: Comparison of the predicted time to loss of ambulation with the best fitting parametric curves fit to the MAIC-weighted givinostat loss of ambulation data**




Abbreviations: KM, Kaplan-Meier; LOA, loss of ambulation; MAIC, matched adjusted indirect comparison.

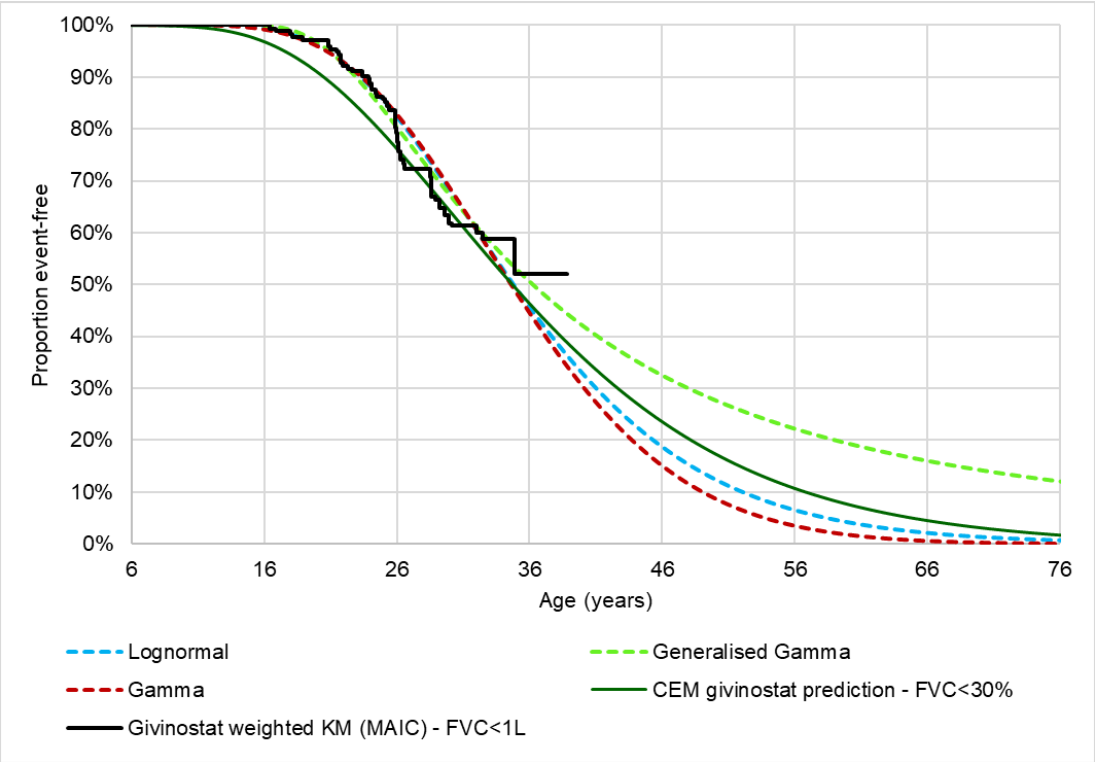
**Figure 45: Comparison of the predicted time to ventilation with the best fitting parametric curves fit to the MAIC-weighted givinostat non-invasive ventilation data**




Abbreviations: KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison; NIV, non-invasive ventilation.


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**Figure 46: Comparison of the predicted time to FVC<30% with the best fitting parametric curves fit to the MAIC-weighted givinostat FVC<1L data**




Abbreviations: FVC, forced vital capacity; KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison.

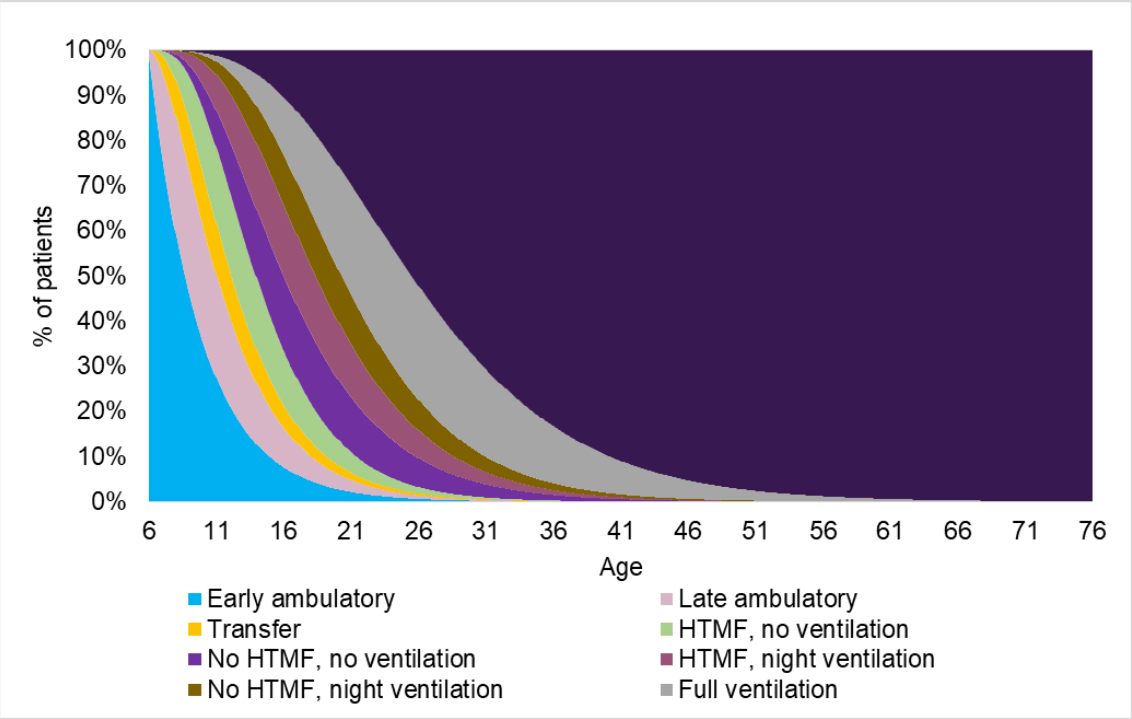
### *B.3.3.3* Summary of health state membership

This Section summarises the predictions of health state membership by the CEM; Section B.3.12 provides further validation of the CEM predictions.

Figure 47 and Figure 48 present the health state membership for ECM and givinostat, respectively. Table 53 presents the average time spent in each health state (undiscounted) for ECM and givinostat. Table 54 presents the median age patients are predicted to reach key disease milestones.

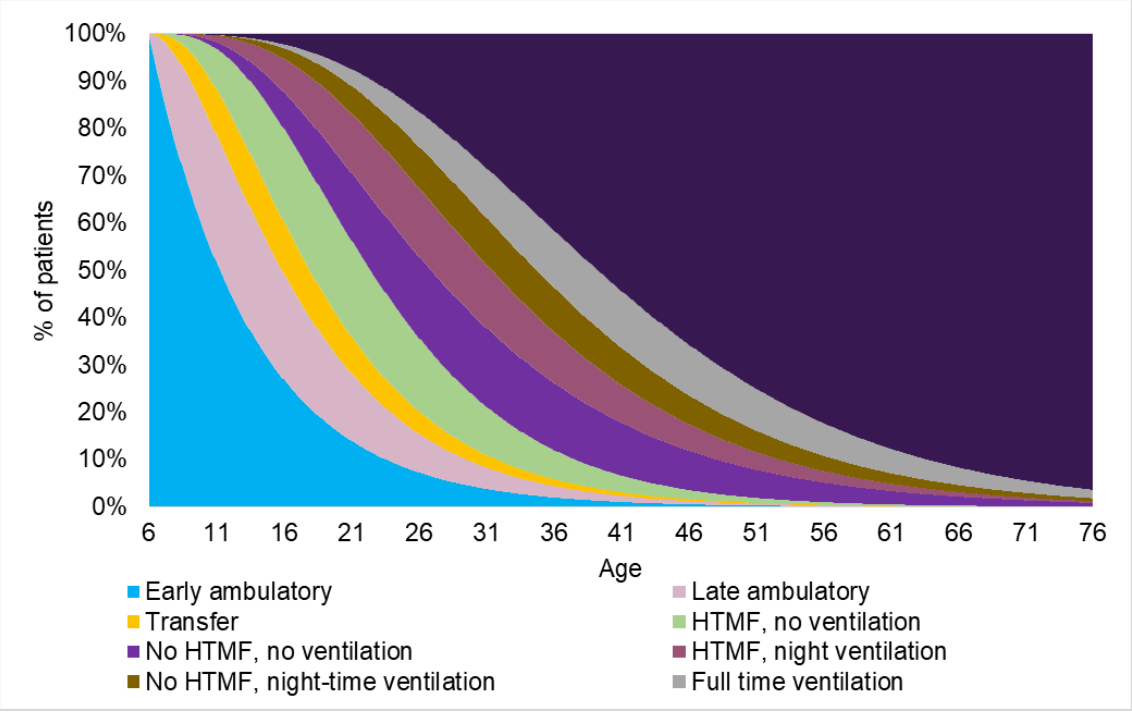

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**Figure 47: Health state membership for ECM**




Abbreviations: ECM, established clinical management; HTMF, hand-to-mouth function.

**Figure 48: Health state membership for givinostat**




Abbreviations: ECM, established clinical management; HTMF, hand-to-mouth function.


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**Table 53: Average time spent in each health state (undiscounted)**

| | Average time in state (years) | ECM | Givinostat |
|---|---|---|---|
| 1 | Early ambulatory | 3.9 | 7.7 |
| 2 | Late ambulatory | 2.2 | 4.4 |
| 3 | Transfer | 1.0 | 2.0 |
| 4 | HTMF, no ventilator | 1.8 | 4.4 |
| 5 | No HTMF, no ventilator | 2.4 | 5.4 |
| 6 | HTMF, night ventilator | 2.3 | 4.1 |
| 7 | No HTMF, night vent | 1.9 | 3.2 |
| 8 | Full time ventilation | 5.6 | 4.2 |

Abbreviations: ECM, established clinical management; HTMF, hand-to-mouth function.

**Table 54: Median age at disease milestones**

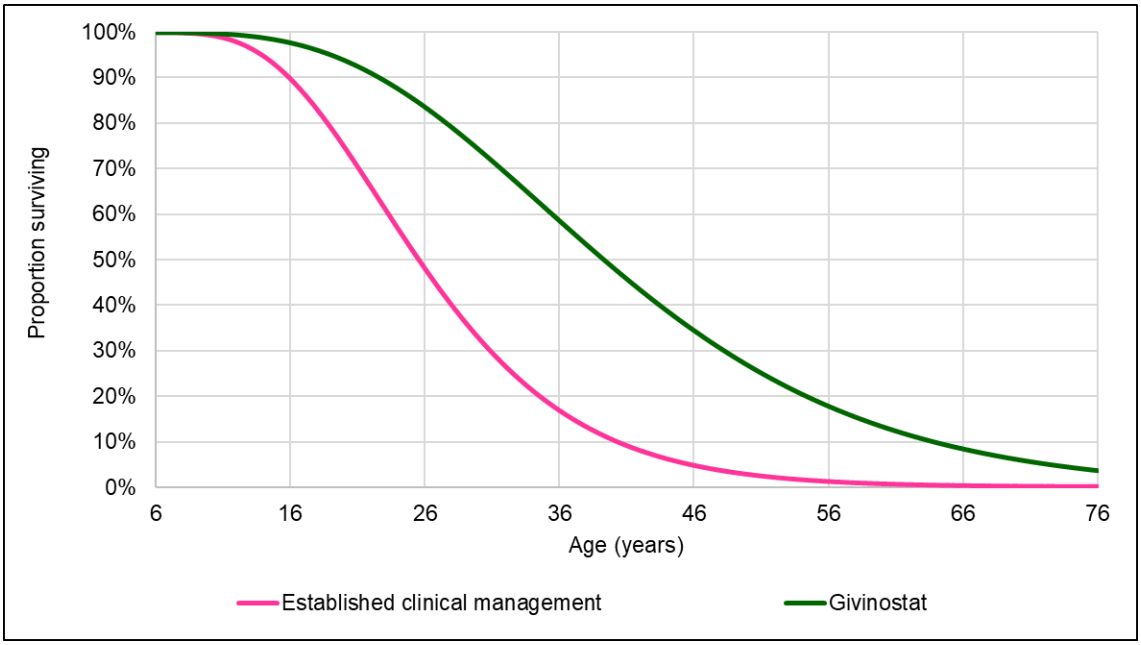
| | ECM | Givinostat |
|---|---|---|
| Unable to stand from supine | 8.7 | 11.3 |
| Loss of ambulation | 12.1 | 17.9 |
| Loss of HTMF | 15.8 | 26.0 |
| Starting ventilation | 16.0 | 26.9 |
| Starting full-time ventilation | 20.3 | 34.8 |
| Death | 25.4 | 39.3 |

Abbreviations: ECM, established clinical management; HTMF, hand-to-mouth function.

Figure 49 compares the predicted survival for ECM and givinostat. Table 55 presents the median survival and landmark survival estimates. The improvement in survival predicted by the CEM for givinostat is driven by delays in transitioning through the health states.


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**Figure 49: Predicted survival for ECM and givinostat**




Abbreviations: ECM, established clinical management; NHM, natural history model.

**Table 55: Predicted survival for ECM and givinostat**

| | ECM | Givinostat |
|---|---|---|
| **Median age** | 25.4 | 39.3 |
| **% surviving at (age):** | | |
| **10** | 99.4% | 99.8% |
| **20** | 74.6% | 93.8% |
| **30** | 32.6% | 74.2% |
| **40** | 10.3% | 48.2% |
| **50** | 2.8% | 26.7% |
| **60** | 0.7% | 13.2% |
| **70** | 0.1% | 6.0% |

Abbreviations: ECM, established clinical management.

### *B.3.3.4* Treatment duration

**Givinostat**

In EPIDYS, seven patients discontinued givinostat (5.9%) due to consent withdrawn (n=4, 3.4%) and AEs (n=3, 2.5%) across the 18 month follow-up. In the OLE study, 21 patients discontinued givinostat (10.1%) due to AEs (8, 3.9%), consent withdrawn (n=7, 3.4%), other reasons (n=4, 1.9%), and lost to follow-up (n=2, 1.0%) across the 39.6 month (1,204.2 days) follow-up. In the base case, the CEM estimates the discontinuation rate each cycle based on a weighted exponential function calculated based on the EPIDYS and OLE data i.e., lambda


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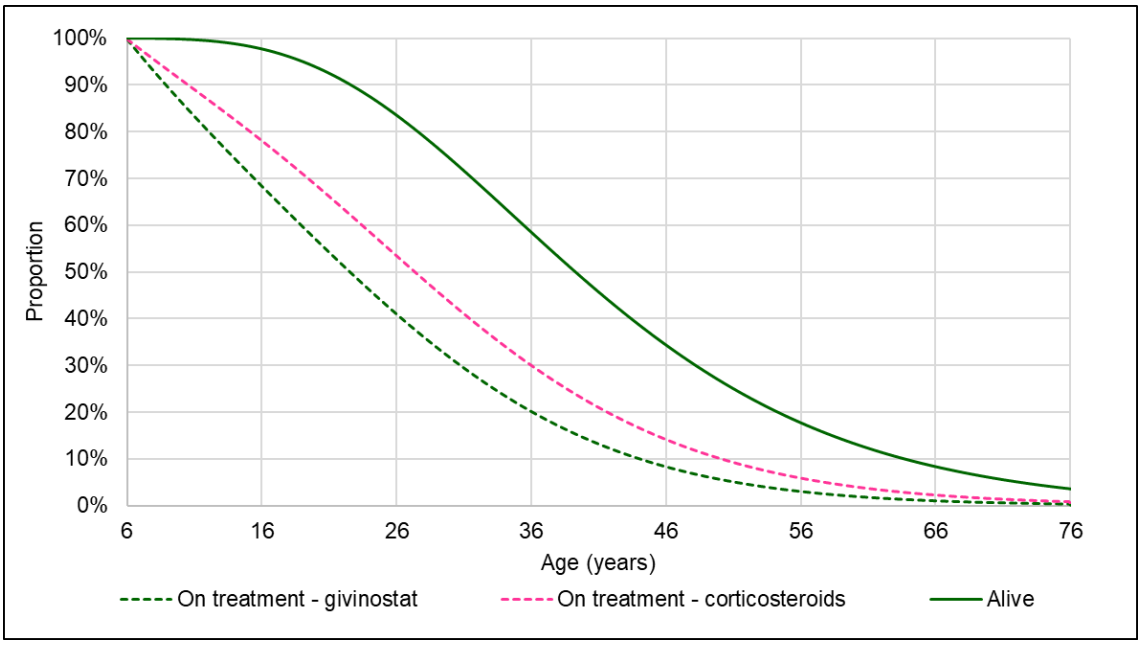
= 0.0030 = % EPIDYs x [-LN(1-(7/118))/18)] + % OLE x [-LN(1-(21/207))/39.6)]. A scenario analysis considers the impact of using data from EPIDYS only.

As the discontinuation data from the givinostat studies are immature and only two deaths occurred within the EPIDYS and the OLE follow-ups, the discontinuation rate is multiplied by the proportion of patients predicted to be alive each cycle in the CEM to reflect the impact of survival on treatment discontinuation over time.

Based on UK clinical feedback, no explicit treatment continuation rule is assumed for givinostat in the base case. Scenario analyses explore the impact of continuing treatment with givinostat until patients require full-time ventilation, lose HTMF, and lose ambulation.

As explained in Section B.3.2.3, it is assumed that givinostat will not impact the CS use comprising ECM. Therefore, treatment duration for CS in the givinostat arm is modelled as per the ECM arm (Section B.3.2.3). Figure 50 presents the treatment duration with givinostat and CS in the givinostat arm over time. Table 56 presents the proportion on treatment compared to survival.

**Figure 50: Treatment duration with givinostat and CS | givinostat**




Abbreviations: CS, corticosteroids.


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**Table 56: Treatment duration with givinostat and CS | givinostat**

| | Givinostat | |
|---|---|---|
| | **Givinostat** | **CS** |
| **Median treatment duration** | 16.5 years | 21.3 years |
| **Proportion on-treatment at (age):** | | |
| **10** | 86.5% | 91.2% |
| **20** | 57.0% | 68.7% |
| **30** | 31.6% | 43.4% |
| **40** | 14.4% | 22.6% |
| **50** | 5.6% | 10.0% |
| **60** | 1.9% | 4.0% |
| **70** | 0.6% | 1.4% |

Abbreviations: CS, corticosteroids.

For patients who discontinue treatment with givinostat, the CEM assumes health state transitions remain the same as for patients continuing to receive givinostat. This is a conservative assumption; the transitions in the givinostat arm only reflect a treatment effect for age at loss of ambulation. For longer-term outcomes driven by age at non-invasive ambulation and age at FVC<30%, the estimated benefit in the MAICs is based on the improvement observed for age at loss of ambulation and the assumption that this will translate to longer-term benefits, regardless of ongoing treatment with givinostat.

In the CEM and ITCs, the relationship between age at loss of ambulation and longer-term outcomes is informed by the UK real-world data (Section B.2.8) and supported by the literature. McDonald et al. 2018a investigated the relationship between NSAA and time to rise from supine/floor and loss of ambulation; both higher NSAA scores and lower time to rise from supine/floor were associated with later age at loss of ambulation.[209] This study also demonstrates the relationship between FVC and the Brooke Scale; successive loss of upper extremity function correlated strongly with pulmonary function progressive loss – aligning with Lee et al. 2016 confirming that upper limb function is highly correlated with FVC values.[210] Humbertclaude et al. 2012 find that age at loss of ambulation is predictive of both the age at which the peak FVC is realised, and the absolute peak obtained FVC.[186] These findings are supported by McDonald et al. 2018b who demonstrate age at loss of ambulation predicts time to an absolute FVC of 1 L and Levine et al. 2023 who show that the decline in percentile predicted FVC and total lung capacity correlate with age and loss of ambulation.[187, 188]

These data describe the relationship between earlier outcomes and longer-term outcomes for patients receiving ECM. Assuming the same relationship holds for givinostat as for ECM is conservative for two reasons:

- Firstly, improving the skeletal muscle integrity/function and delaying the loss of ambulation, as observed with givinostat in EPIDYS and the OLE study, may have an exaggerated impact on longer-term outcomes.


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- Secondly, continued treatment with givinostat may lead to a treatment effect above and beyond what we would expect to see translating from delaying the loss of ambulation.

Nevertheless, the treatment effect of givinostat on these longer-term outcomes is unknown. Therefore, the CEM assumes that the relationships between age at loss of ambulation and the longer-term outcomes are the same for givinostat as those observed for ECM. This means that no treatment effect is assumed beyond age at loss of ambulation i.e., it is expected that the delay in loss of ambulation will translate to improved outcomes regardless of the ongoing givinostat treatment. This aligns with assuming health state transitions remain the same for patients in the givinostat arm, regardless of ongoing treatment.

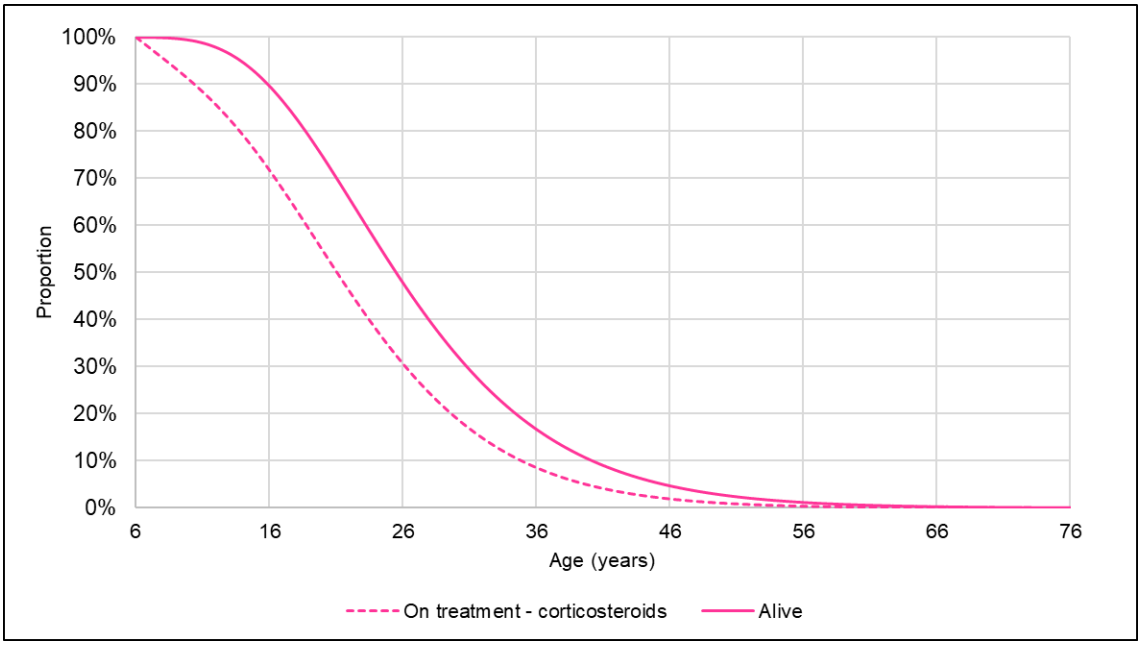
**Established clinical management**

As described in Section B.3.2.3, ECM comprises oral CS, including prednisone or deflazacort – aligning with the EPIDYS clinical trial. In EPIDYS, two patients discontinued the placebo arm (3.3%) due to consent withdrawn across the 18-month follow-up. In the base case, the CEM estimates the discontinuation rate each cycle based on an exponential function calculated from the EPIDYS data (lambda = 0.0019 = -LN(1-(2/61))/18).

In line with the rationale presented for givinostat, no explicit treatment continuation rule is assumed for CS in the base case. Scenario analyses explore the impact of continuing treatment with CS until the patients require fulltime ventilation, lose HTMF, and lose ambulation.

Figure 51 presents the treatment duration compared to survival with CS in the ECM arm over time. Table 57 presents the proportion on treatment compared to survival.

**Figure 51: Treatment duration with CS | ECM**




Abbreviations: CS, corticosteroids; ECM, established clinical management.


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**Table 57: Treatment duration with CS | ECM**

| | CS |
|---|---|
| **Median treatment duration** | 15.0 years |
| **Proportion on-treatment at (age):** | |
| **10** | 90.8% |
| **20** | 54.6% |
| **30** | 19.1% |
| **40** | 4.8% |
| **50** | 1.0% |
| **60** | 0.2% |
| **70** | 0.0% |

Abbreviations: CS, corticosteroids; ECM, established clinical management.

For patients who discontinue treatment with CS, the CEM continues to use the transitions estimated from the updated NHM (analysis 2; see Section B.3.3.1). The updated NHM reflects transitions of patients receiving ECM; these data reflect ECM including patients discontinuing and continuing treatment with CS over time.

### *B.3.3.5* Co-morbidities

Once children lose ambulation, care is taken to closely monitor their spines and heart. The spine develops scoliosis i.e. curvature of the spine, which needs its own management and may require scoliosis surgery. As scoliosis progresses, it may have a significant impact on the respiratory system and affect positioning and comfort in a wheelchair.[211] As a result, most patients with scoliosis undergo spinal fusion surgery.[212] The heart develops cardiomyopathy, a disease of the heart muscle which makes it harder for the heart to pump blood to the rest of the body and can lead to heart failure, which may need treatment with angiotensin converting enzyme inhibitors and beta blockers. The impact of comorbidities (scoliosis and cardiomyopathy) on disease progression or mortality is assumed to be reflected in the transition probabilities from the updated NHM. Similarly, the impact of comorbidities on costs and HRQoL is assumed to be reflected in health-state costs and utilities, respectively.

However, it is anticipated that treatment with givinostat will reduce the number of patients who require spinal fusion surgery beyond the impact reflected by the health state costs and utilities. Delaying the loss of ambulation, as observed in patients treated with givinostat, may avoid the period of growth in adolescents, during which the progression of scoliosis is fastest.[213] Therefore, the need for surgery in future health states may be reduced. To reflect the anticipated benefit from reduced spinal fusion surgeries in the givinostat arm, the CEM includes the respective costs and utility decrements in addition to health state costs and utilities.

Pietrusz et al. 2023 report the findings from a multicentre retrospective case note review, conducted between three UK hospitals (London, Newcastle, and Oxford).[40] Note: these patients correspond to the dataset informing the unpublished UK real-world data used in the ITCs (Section B.2.8) and the updated NHM (Section B.3.3.1). The data indicate 51.4%


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(18/35) and 30.2% (19/63) of patients required scoliosis surgery across CS stopped and CS continued treatment arms, respectively. Based on this, the CEM assumes 37.8% (18+19)/(35+63) of patients in the ECM arm receive scoliosis surgery.

No cases of scoliosis surgery are observed in patients treated with givinostat in EPIDYS or the OLE study. As reported in McDonald et al. 2018, scoliosis surgery is assumed on average four years following loss of ambulation.[187] Therefore, the data from the givinostat studies may not be sufficiently mature to conclude on the relative reduction in scoliosis surgery. As a conservative approach, the CEM assumes that the loss of ambulation HR for givinostat vs. ECM i.e. 0.51 is applied to the scoliosis surgery rate with ECM. This results in 14.8% of patients receiving scoliosis surgery in the givinostat arm.

In the CEM, spinal fusion surgery is assumed on average four years following loss of ambulation and patients are eligible for spinal surgery in the CEM from 15–25 years - aligned with data from McDonald et al. 2018 and assumptions in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135).[130]

#### *B.3.3.6* Adverse events

In EPIDYS and the OLE study, treatment-related AEs were defined as an adverse event that started or worsened after the start of administration of study drug. Table 58 presents the number of treatment-related AEs occurring in ≥5% of boys in either treatment arm observed in the ITT population from EPIDYS and the OLE study. Treatment-related AEs are shown to reduce in the OLE study compared with EPIDYS. This is consistent with Section B.2.9.1 where treatment-related AEs are shown to reduce over time.[140]
In the base case, the weighted monthly proportions for treatment-related AEs (shown in Table 58) from the EPIDYS and OLE studies are applied in the CEM:

- Monthly AE proportions reflecting the givinostat arm from the EPIDYS and OLE data are applied to patients receiving treatment with givinostat in the givinostat arm. Following discontinuation of givinostat, monthly AE proportions reflecting the placebo arm from the EPIDYS data are applied to patients continuing to receive CS in the givinostat arm. No treatment-related AEs are assumed for patients who have discontinued givinostat and CS.

- Monthly AE proportions reflecting the placebo arm from the EPIDYS data are applied to patients receiving CS in the ECM arm. No treatment-related AEs are assumed for patients who have discontinued CS.

A scenario analysis considers the impact of using the EPIDYS data only for AEs in the givinostat arm. Note: as treatment-related AEs are expected to reduce over time for givinostat, use of the EPIDYS and OLE data across the entire treatment duration is a conservative assumption within the CEM.


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**Table 58: Number and monthly proportion of treatment-related AEs from EPIDYS and the OLE study**

| | EPIDYS | | OLE study | Weighted givinostat |
|---|---|---|---|---|
| | Givinostat | Established clinical management | Givinostat | |
| **N** | 118 | 61 | 207 | NA |
| **Follow-up (months)** | 18 | 18 | 39.6 (1,204.2 days) | NA |
| **Treatment-related AEs, n (monthly proportion per patient)** | | | | |
| **Decreased platelets count** | 20 (0.9%) | 0 (0%) | 29 (0.4%) | 0.6% |
| **Thrombocytopaenia** | 19 (0.9%) | 0 (0%) | 33 (0.4%) | 0.6% |
| **Increased blood triglyceride concentration** | 14 (0.7%) | 3 (0.3%) | 41 (0.5%) | 0.6% |
| **Hyperglyceridaemia** | 13 (0.6%) | 1 (0.1%) | 19 (0.2%) | 0.4% |
| **Diarrhoea** | 25 (1.2%) | 2 (0.2%) | 40 (0.5%) | 0.7% |
| **Abdominal pain** | 16 (0.8%) | 2 (0.2%) | 16 (0.2%) | 0.4% |
| **Upper abdominal pain** | 9 (0.4%) | 1 (0.1%) | 10 (0.1%) | 0.2% |
| **Vomiting** | 7 (0.3%) | 0 (0%) | 8 (0.1%) | 0.2% |

Abbreviations: AE, adverse events; ECM, established clinical management; N, number; OLE, open-label extension.

Long-term CS use in DMD is associated with side effects which are not yet observed across EPIDYS and the OLE study follow-ups. Weight gain, growth retardation, and Cushingoid features are the most seen side effects when long-term CS are given to children.[214] Other notable side effects include behavioural changes, broken bones, tiredness, physical appearance, delayed puberty, gastrointestinal issues, and adrenal crisis.[129]

There are limited data quantifying the impact of long-term CS use in DMD in the literature; two studies were identified in a recent literature review published in 2017.[215, 216] These studies were from 1991 and 2002. Feedback from UK clinical experts at the June 2024 advisory board indicated that clinical practice has evolved in the last 20 years, with the management of side effects associated with long-term CS use having improved. Therefore, these data are not relevant to current UK clinical practice. Due to lack of data on the burden of long-term CS use, these side effects are not included in the CEM. However, as givinostat is not anticipated to change CS use in patients with DMD, the side effects relating to CS use would be similar in both arms. Therefore, this assumption is not anticipated to impact cost-effectiveness results.

## *B.3.4 Measurement and valuation of health effects*

### B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality of life (HRQoL) data were collected in the EPIDYS clinical trial at baseline, week 48, and week 72 using the paediatric outcomes data collection instrument (PODCI). HRQoL data are being collected in the OLE study at Week 48 and then yearly using PedsQL in children and SF-36 in adults. All measures can be completed by parents or


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patients. Section B.2.6.3 and B.2.6.6 detail the results of the PODCI and PedsQL collected in EPIDYS and the OLE study, respectively. SF-36 data are too limited at this stage to draw any conclusions.

The EQ-5D is the preferred measurement tool as per the NICE manual.[200] However, EQ-5D data were not collected in the givinostat studies. Additionally, to date, no mapping algorithm exists mapping from the PODCI to the EQ-5D. Although there are mapping algorithms published to map from the PedsQL to the EQ-5D, mapping was not conducted to avoid the additional uncertainty associated with this approach.[217–219] Therefore, the utilities in the CEM are sourced from published studies.

### B.3.4.2 Mapping

No mapping was undertaken.

### B.3.4.3 Health-related quality-of-life studies

HRQoL data have been identified from an SLR, the Project HERCULES BOI study, and a UK caregiver vignette study commissioned by Pfizer.[98, 193] A summary of the relevance of each of these sources for the CEM is presented below. Following this, the relevant Sections describe each of the sources in more detail.

The SLR identified 25 studies, of which five reported EQ-5D data for patients stratified by health state: Audhya et al. 2023, Szabo et al. 2023, Castro et al. 2023, Andreozzi et al. 2022, and Crossnohere et al. 2021.[34, 95, 220–222] One study reported EQ-5D data for caregivers stratified by health state: Landfeldt et al. 2017.[192]

Audhya et al. 2023 informs patient utilities in the base case. The measurements align with the health states specified in the CEM and the methods for determining utilities align with the NICE reference case i.e. the EQ-5D measure was used and self-reported by patients.[95] This study is also the most recent patient HRQoL data available in DMD. Limitations associated with this study relate to the EQ-5D-5L instrument being used, rather than the NICE preferred EQ-5D-3L, and the study being based in the US with utilities derived from the US tariff.

Szabo et al. 2023 only report utility values for one health state. Therefore, these data are not considered in the CEM.[220] Castro et al. 2023 and Andreozzi et al. 2022 report utility values based on the Spanish and Portuguese tariffs, respectively.[34, 221] These values appear much lower than other identified studies, with negative values reported for later health states. Therefore, whilst these studies are considered supportive of the inputs informing the CEM - utilities are shown to decline across the progression health states – these studies are not considered in the CEM. However, these studies highlight that the patient utilities informing the CEM may be conservative.

Although the values reported in Crossnohere et al. 2021 are supportive of the outcomes presented in Audhya et al. 2023 – utilities are shown to decline across the progressing health states and the values reported for the non-ambulatory health states are very similar - these values are not considered within the CEM as HRQoL was proxy-reported by caregivers for patients aged <18.[222] Feedback from clinical experts at the June 2024 advisory board indicated that the perspective is important when assessing patient HRQoL and that values proxy-reported by caregivers would likely differ from self-reported patient


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values.[20] This is supported by the differing utility values reflecting the three perspectives considered in the study (adult with DMD, caregiver of an adult, and caregiver of a minor). This is further supported by Szabo et al. 2023 who compare EQ-5D utility values measured by the patient and caregiver for the same health states and find different values depending on perspective.

The values reported in Landfeldt et al. 2017 are further supportive of the outcomes presented in Audhya et al. 2023 - utilities are shown to decline across the progressing health states and the values reported are very similar.[192] However, patient utilities were measured using the HUI-3 and proxy-reported by caregivers. Therefore, this is considered unsuitable as a base case. Nevertheless, due to the case precedence of use of the Landfeldt et al. 2017 study in ongoing and previous NICE appraisals in DMD (vamorolone [GID-TA11135] and ataluren [HST22]), the values reported in this study are explored in a scenario analysis.[7, 130] The output from the unpublished Project HERCULES BOI study is also considered in a scenario analysis.

The UK caregiver vignette study informs caregiver utilities in the base case. The measurements align with the health states specified in the CEM and the estimated health state utilities align with expectations of caregiver HRQoL across the progression of DMD. Additionally, the study uses time-trade-off (TTO) methodology which may be more sensitive to the challenges faced by caregivers of people with DMD e.g., high levels of stress, significant physical demands, and considerable social and financial strains, which may not be fully reflected by the EQ-5D. A scenario analysis explores the impact of applying the caregiver utilities measured using the EQ-5D and reported in Landfeldt et al. 2017.

**Health-related quality-of-life SLR**

An SLR was conducted to identify relevant published HRQoL evidence in patients with a diagnosis of DMD. Searches were conducted through May and June 2024, and updated in November 2024. The methodology undertaken is described in Appendix H, which details the search strategy, eligibility criteria applied, and full list of identified references. A total of 25 publications were included in the HRQoL SLR from the database searches, grey literature searches, and hand searching.

Appendix H details the 25 identified publications. Of the 25 identified studies, 12 collected HRQoL data using the EQ-5D. Of the 12 studies reporting EQ-5D data, five reported on patient HRQoL stratified by health state, five reported on patient HRQoL overall, and two reported on one analysis of caregiver HRQoL which stratified utilities by health state. Table 59 summarises the studies identified reporting EQ-5D data on patient and/or caregiver HRQoL stratified by health state.


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**Table 59: Studies assessing utility values in patients with DMD**

| Citation | Study design | Objective | Countries | Data source | Utilities | Respondents | Mean age | EQ-5D measure |
|---|---|---|---|---|---|---|---|---|
| Audhya et al. 2023[95] | Web-based survey | HRQoL impact of DMD | US | Parent Project Muscular Dystrophy, an advocacy group in the US | Patient | N=63<br>Males with DMD aged 12–40 years | 19.8 (6.1) | EQ-5D-5L, US tariff |
| Szabo et al. 2023[220] | Cross-sectional | Patient- and caregiver-derived utility values for DMD health states | US | US-based patient organization | Patient | N=31 patient-caregiver dyads | 14 (5.9) | EQ-5D, level and tariff NR |
| Castro et al. 2023[221] | Cross-sectional | Interim analysis from Project HERCULES BOI study in US and Spain | US and Spain | Male patients diagnosed with DMD at least 12 months before date of consultation (index date), prospectively recruited by neuromuscular physicians in specialist DMD centres | Patient | N=56 Caregiver and patient (for patients with cognitive delay or below 16 years, caregivers were asked to complete the study on the patient's behalf) | 16.9 (8.8) | EQ-5D-5L, Spanish tariff |
| Andreozzi et al. 2022[34] | Cross-sectional | HRQoL of DMD patients | Portugal | Portuguese Neuromuscular Association | Patient | N=46 caregivers | 18.9±8.2 | EQ-5D-3L, Portuguese tariff |
| Crossnohere et al. 2021[222] | Cross-sectional | Assess the appropriateness of the EQ-5D in DMD | Australia, Belgium, Canada, Netherlands, UK, US | International patient advocacy groups | Patient | N=61 adults with DMD<br>Males ≥18-years with DMD | 28.2 (18-48) | EQ-5D-3L, US tariff |
| | | | | | | N=134<br>Caregivers ≥18-years of a male | 42.4 (23-65) | EQ-5D-3L, US tariff |


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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | <18-years with DMD | | |
| | | | | | | N=68<br>Caregivers ≥18-years of a male ≥18-years with DMD | 54.9<br>(40– 70) | EQ-5D-3L, US tariff |
| Landfeldt et al. 2016, Landfeldt et al. 2017[45, 192] | Cross-sectional | Burden among caregivers of patients with DMD | Germany, Italy, UK, US | TREAT-NMD | Caregivers | Caregivers of males with DMD aged ≥ 5 years | 44 (39–50) | EQ-5D, UK tariff |

Abbreviations: BOI, burden of illness; DMD, Duchenne muscular dystrophy; EQ-5D, EuroQol 5-dimensions; HRQoL, health-related quality of life; NR, not reported.


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Audhya et al. 2023 estimate utility values for clinical and functional health states in DMD, based on patient-reported health status.[95] Study participants with DMD (aged 12-40) were recruited through Parent Project Muscular Dystrophy, an advocacy group in the US. A survey was developed using a web-based platform to capture self-reported data from study participants. The survey included a clinical questionnaire to document the extent and severity of DMD symptoms, a series of demographic questions to help characterize the study population, as well as a series of validated preference-based measures of HRQoL, including the HUI and EQ-5D (5-level [5L] version). Utilities were derived using a US-specific value set. Table 60 presents the mean EQ-5D-5L utility values by health state.

**Table 60: Utility values sourced from Audhya et al. 2023[95]**

| | N | EQ-5D-5L |
|---|---|---|
| **Early ambulatory** | 11 | 0.79 (0.20) |
| Preserved upper limb, no daytime ventilation, without symptomatic cardiomyopathy | 10 | 0.84 (0.13) |
| Mildly impaired upper limb, no daytime ventilation, without symptomatic cardiomyopathy | 1 | 0.30 (NA) |
| **Late ambulatory** | 8 | 0.64 (0.30) |
| Transitional, preserved upper limb, no daytime ventilation, without symptomatic cardiomyopathy | 6 | 0.59 (0.33) |
| Transitional, mildly impaired upper limb, no daytime ventilation, without symptomatic cardiomyopathy | 2 | 0.79 (0.16) |
| **Early non-ambulatory** | 21 | 0.31 (0.13) |
| Preserved upper limb, no daytime ventilation, without symptomatic cardiomyopathy | 2 | 0.46 (0.10) |
| Mildly impaired upper limb, no daytime ventilation, without symptomatic cardiomyopathy | 16 | 0.30 (0.14) |
| Mildly impaired upper limb, no daytime ventilation, with symptomatic cardiomyopathy | 3 | 0.29 (0.07) |
| **Late non-ambulatory** | 23 | 0.22 (0.15) |
| Moderately impaired upper limb, no daytime ventilation, without symptomatic cardiomyopathy | 9 | 0.22 (0.15) |
| Moderately impaired upper limb, no daytime ventilation, with symptomatic cardiomyopathy | 4 | 0.27 (0.08) |
| Moderately impaired upper limb, nighttime, and daytime ventilation, without symptomatic cardiomyopathy | 5 | 0.25 (0.14) |
| Loss of upper limb function, no daytime ventilation, without symptomatic cardiomyopathy | 1 | 0.26 (NA) |
| Loss of upper limb function, nighttime, and daytime ventilation, without symptomatic cardiomyopathy | 2 | 0.26 (0.01) |
| Loss of upper limb function, nighttime, and daytime ventilation, with symptomatic cardiomyopathy | 2 | 0.02 (0.34) |

Szabo et al. 2023 reported only two utility values measured by the EQ-5D (level not reported) measured by the patient and by the caregiver, for a non-ambulatory, mildly impaired upper limb function, without ventilation and without symptomatic cardiomyopathy health state.[220] The values were 0.30 and 0.15, respectively.


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Castro et al. 2023 report on the EQ-5D-5L values collected as part of a Project HERCULES BOI study focusing on patients from the US and Spain.[221] Patients were prospectively recruited by neuromuscular physicians in specialist DMD centres during regular consultation. The sample consisted of 207 patients with 118 (57%) in the US and 89 (43%) in Spain. Utility values were derived using the EQ-5D-5L Spanish value set (see Table 61).

**Table 61: Utility values sourced from Castro et al. 2023[221]**

| Disease Stage | EQ-5D-5L utility value |
|---|---|
| Early ambulatory | 0.60 |
| Late ambulatory | 0.62 |
| Transfer | 0.58 |
| HTMF, no ventilation | 0.39 |
| No HTMF, no ventilation | 0.27 |
| HTMF, nighttime ventilation | 0.06 |
| No HTMF, nighttime ventilation | -0.02 |
| Full time ventilation | -0.39 |

Andreozzi et al. 2022 report on a cross-sectional study assessing patients' HRQoL using the EQ-5D-3L as reported by their caregivers.[34] The study recruited patients and caregivers from the Portuguese Neuromuscular Association and utility values were derived using a Portuguese value set. A total of 46 DMD main caregivers completed the questionnaires. Overall, DMD patients had a low HRQoL, with a mean utility value of 0.05 (SD=0.33). The utility value for non-ambulant patients was −0.05 (SD=0.24) and for ambulant patients was 0.51 (SD=0.28). Patients with full-time ventilation had the lowest mean utility value (−0.20; SD=0.22), followed by patients with non-full-time ventilation support (−0.05; SD=0.21) and no ventilation support (0.03; SD=0.29).

Crossnohere et al. 2021 reported EQ-5D-3L and EQ-VAS data collected from an international, cross-sectional sample of adults with DMD and caregivers of patients with DMD.[222] Adults with DMD completed the self-reported version of the measure (EQ-5D-3L) while caregivers completed proxy versions (EQ-5D-Proxy1 if patient was 12 y and older or EQ-5D-Y if patient was 11 y and younger). Utilities were obtained using a US tariff. Table 62 presents the utility values by age, role, and disease status reported in the paper.

**Table 62: Utility values sourced from Crossnohere et al. 2021[222]**

| | N | Mean (SD) |
|---|---|---|
| **Patient age, years** | | |
| 9 or younger | 62 | 0.59 (0.21) |
| 10-19 | 94 | 0.42 (0.25) |
| 20-29 | 69 | 0.33 (0.21) |
| 30-39 | 31 | 0.26 (0.16) |
| 40+ | 7 | 0.27 (0.16) |
| **Role** | | |
| Adult with DMD | 61 | 0.40 (0.19) |
| Caregiver of adult | 68 | 0.27 (0.20) |
| Caregiver of minor | 134 | 0.50 (0.25) |


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| | | |
|---|---|---|
| **Disease stage** | | |
| Early ambulatory | 71 | 0.65 (0.17) |
| Late ambulatory | 31 | 0.49 (0.23) |
| Early non-ambulatory | 111 | 0.31 (0.20) |
| Late non-ambulatory | 50 | 0.26 (0.16) |

Landfeldt et al. 2017 considered three state-transition models to evaluate the cost-effectiveness of a hypothetical treatment for DMD compared to ECM in a UK setting.[192] The utility inputs informing the models were based on a cross-sectional, observational study conducted by the authors and published across four publications (Landfeldt et al. 2014, Landfeldt et al. 2015, Landfeldt et al. 2016a and Landfeldt et al. 2016b).[45, 49, 56, 223]

The study assessed caregiver HRQoL using the EQ-5D-3L. EQ-5D utilities were derived using the UK value set, which is based on preference data collected through the time-tradeoff method from 2,997 randomly selected members of the adult general population in England, Scotland, and Wales. For use in the state transition models presented in Landfeldt et al. 2017, the utility data were mapped to the specified model states by fitting generalised linear regression models (GLMs) – as described in Landfeldt et al. 2015. Table 63 presents the resulting utilities used in the published CEMs.

The Landfeldt publications also report on patient HRQoL. These data are shown in Table 63 for comparison with the caregiver utilities and to align with previous NICE submissions in DMD; previous NICE submissions have used the Landfeldt patient utilities either in the base case or in a scenario.[7, 130] However, these data are measured through proxy-assessment by the primary caregivers using the HUI questionnaire. The HUI is a generic HRQoL instrument encompassing 16 questions covering eight dimensions (hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion, and cognition) and has been validated for proxy assessments in ages 5 years and older. Patient utilities were derived using the HUI Mark 3 multi-attribute health status classification system, which is based on preference data collected using the standard gamble method and a visual analogue scale from 256 randomly selected members of the general population in Hamilton, Ontario, Canada.

**Table 63: Utilities sourced from Landfeldt et al. 2017[192]**

| | **Utilities** | |
|---|---|---|
| | **Patient*** | **Caregiver** |
| **Model 1 (DMDSAT)** | | |
| Initial score | 0.879 (0.037) | 0.562 (0.016) |
| Per lost score (multiplier) | 0.905 (1.003) | 0.995 (1.001) |
| **Model II (ambulatory status)** | | |
| Early ambulatory | 0.699 (0.036) | 0.858 (0.017) |
| Late ambulatory | 0.607 (0.029) | 0.839 (0.017) |
| Early non-ambulatory | 0.224 (0.014) | 0.784 (0.021) |
| Late non-ambulatory | 0.146 (0.010) | 0.810 (0.018) |
| **Model III (ventilation status)** | | |
| None | 0.518 (0.027) | 0.837 (0.014) |
| Nighttime | 0.129 (0.017) | 0.775 (0.030) |


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| | | |
|---|---|---|
| Day and nighttime | 0.051 (0.010) | 0.774 (0.033) |

*Collected using the HUI-3.
Abbreviations: DMDSAT, Duchenne muscular dystrophy Functional Ability Self-Assessment Tool.

**BOI health-related quality-of-life study**

In addition to the SLR, a burden of illness (BOI) study has been conducted as part of Project HERCULES – these data have not been published.[193] The BOI study is a retrospective and cross-sectional study, conducted in the UK. The study recruited a sample of N=24 neuromuscular specialists, who were surveyed between January 2020 and October 2020. Specialists were asked to complete a Case Record Form (CRF) for up to ten eligible patients capturing patient characteristics and direct health costs over the last 12 months. Eligible patients had a DMD diagnosis at least 24 months before the index date and carefully read, understood, and signed the informed consent form. Specialists then invited each patient to complete a corresponding Patient and Public Involvement and Engagement (PPIE) questionnaire. Dependent on the age of the patient, the PPIE form was completed by the patient (16 years or older), the patient's primary caregiver (4-7 years old), or a combination of both (8-16 years old). The PPIE provides direct and indirect non-medical cost information, including work loss and out-of-pocket expenses, as well as completion of validated patient reported outcomes measures, including the EQ-5D-5L, DMD-QoL and WPAI. The BOI study aimed to stratify results according to the eight health states published in the NHM – see Section B.3.2.2.

The DMD-QoL is a University of Sheffield produced tool (created as part of Project HERCULES) which measures the HRQoL of patients with DMD, and dependent on age is completed by either the patient (self-complete) or the caregiver (proxy). This consists of 14 questions split into three domains: the physical domain, the social domain, and the physiological domain. These combine to produce a summary score.

The sample included n=197 patients. However, n=68 patients could not be stratified based on disease stage due to lack of relevant data. Therefore, n=129 patients contributed to the analyses. Of the n=129 patients, n=87 had a matched PPIE form (n=49 patient reported and n=38 caregiver reported). The average age across included patients was 14.18. The study obtained responses from the EQ-5D-Y (n=19), EQ-5D-5L (n=24), DMDQoL patient-reported (n=24), DMDQoL caregiver reported (n=16), and CarerQoL-7D (n=35) - Table 64.

The patient utility values derived from the self-reported EQ-5D-5L for patients ≥16-years varied from 0.52 to 0.66. The patient utility values derived from the self-reported DMD-QoL range from 0.33 to 0.54. For all measures explored in the BOI study, insufficient patient numbers were available to ascertain robust patient utility values by health state. Nevertheless, due to the case precedence of use of the BOI study in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135), the values derived from the self-reported DMD-QoL in this study are explored in a scenario analysis for patient utilities.[130]

The costs and resource use data collected as part of this BOI study are presented in Section B.3.5.1 .


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**Table 64: Patient utilities from Project HERCULES BOI study[193]**

| | EQ-5D-Y proxy-reported | | EQ-5D-Y self-reported | | EQ-5D-5L self-reported | | DMD-QoL self-reported | | DMD-QoL proxy-reported | | CarerQoL | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Disease Stage** | **N** | *Mean (SD)* | **N** | *Mean (SD)* | **N** | *Mean (SD)* | **N** | *Mean (SD)* | **N** | *Mean (SD)* | N | Mean (*SD*) |
| **Early ambulatory** | **1** | 0.83 (0) | **14** | 0.79 (0.14) | **0** | NA | **0** | NA | **15** | 0.55 (0.14) | 10 | 86.48 (11.66) |
| **Late ambulatory** | **0** | NA | **1** | 0.63 (0) | **1** | 0.61 (0) | **1** | 0.49 (0) | **1** | 0.41 (0) | 1 | 55.4 (0) |
| **Transfer** | **0** | NA | **1** | 0.6 (0) | **2** | 0.52 (0.14) | **2** | 0.38 (0.1) | **1** | 0.48 (0) | 1 | 84.2 (0) |
| **HTMF, no ventilation** | **0** | NA | **1** | 0.7 (0) | **2** | 0.64 (0.03) | **2** | 0.54 (0.19) | **1** | 0.63 (0) | 3 | 93.9 (5.6) |
| **No HTMF, no ventilation** | **0** | NA | **0** | NA | **8** | 0.62 (0.02) | **8** | 0.51 (0.05) | **0** | NA | 8 | 84.68 (7.28) |
| **HTMF, night-time ventilation** | **0** | NA | **0** | NA | **5** | 0.59 (0.22) | **5** | 0.53 (0.16) | **0** | NA | 5 | 84.56 (4.34) |
| **No HTMF, night-time ventilation** | **0** | NA | **0** | NA | **4** | 0.66 (0.01) | **4** | 0.52 (0.15) | **0** | NA | 4 | 85.73 (7.8) |
| **Full time ventilation** | **0** | NA | **2** | 0.68 (0.07) | **2** | 0.54 (0.29) | **2** | 0.33 (0.04) | **2** | 0.36 (0.19) | 3 | 79.1 (12.7) |
| **Overall** | **1** | 0.83 (0) | **19** | 0.76 (0.13) | **24** | 0.61 (0.12) | **24** | 0.49 (0.12) | **20** | 0.53 (0.15) | 35 | 84.76 (10.12) |

Abbreviations: BOI, burden of illness; HTMF, hand to mouth function; NA, not available; SD, standard deviation.


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**UK caregiver vignette study**

In addition to the SLR, a UK caregiver vignette study was commissioned by Pfizer – these data have not been published.[98] This study aimed to generate health-state utility values for caregivers of people with DMD with sufficient granularity required to differentiate between the DMD health states reported in the Project HERCULES NHM.

Eight DMD caregiver vignettes based on health states defined by the Project HERCULES model were developed. The study involved online interviews with members of the public residing within the UK and recruited via a specialist recruitment agency. The recruitment team aimed to mirror as closely as possible the latest published demographics of the UK according to the Office of National Statistics. A total of 200 participants were interviewed. The mean (standard deviation) age of participants was 44.0 (14.3) years old and 51% were female. Participants were recruited between September and December 2023.

Participants were sent vignettes detailing the progression of DMD across the eight health states, in addition to two vignettes representing full health and dead. As part of the TTO interviews, participants were also asked to complete vignette ranking and rating exercises. Ranking involved organizing vignettes from best to worst, while the rating exercise involved assuming a numerical value from a visual analogue score (VAS) to each vignette. Participants then completed the main TTO exercise for the eight vignettes depicting DMD health states from the caregiver perspective. The TTO exercise required participants to trade off a portion of remaining life expectancy to avoid a hypothetical health state. Mean VAS and utility scores were calculated for each health state from the rating and TTO exercises, respectively.

Table 65 presents the mean utility values as obtained from the TTO approach evaluating vignettes detailing the progression of DMD across the eight DMD health states. The utility scores reflect the progression of the disease with higher mean utility scores in ambulatory stages (health state [1] [HS1]=0.72; HS2=0.67; HS3=0.58) compared to later non-ambulatory stages of the disease (HS4=0.56; HS5=0.50; HS6=0.54; HS7=0.51; HS8=0.48). The VAS scores followed a similar pattern. These mean utility values demonstrate a continuous, nearly linear decline in caregivers' HRQoL, attributed to the escalating demands of their caregiver responsibilities. These data reveal that the HRQoL significantly diminishes not only for patients, but also their caregivers, thereby impacting the broader family and social unit. The UK caregiver vignette study informs caregiver utilities in the base case.

**Table 65: Caregiver utilities from the UK vignette study[98]**

| Health state | Utility value (SD) |
|---|---|
| **Early ambulatory** | 0.72 (0.35) |
| **Late ambulatory** | 0.67 (0.38) |
| **Transfer** | 0.58 (0.43) |
| **HTMF, no ventilation** | 0.56 (0.42) |
| **No HTMF, no ventilation** | 0.50 (0.47) |
| **HTMF, night-time ventilation** | 0.54 (0.45) |
| **No HTMF, night-time ventilation** | 0.51 (0.45) |
| **Full time ventilation** | 0.48 (0.48) |


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Abbreviations: HTMF, hand to mouth function; SD, standard deviation.

### B.3.4.4 Comorbidities

As discussed in Section B.3.3.5, the CEM reflects costs and utilities relating to spinal fusion surgery in addition to health state effects. The CEM assumes a utility decrement of -0.0700 applied for one year – in line with the assumptions in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135) and Matza et al. 2014.[130, 224]

### B.3.4.5 Adverse reactions

Utility decrements are applied, for a specified duration, to treatment-related AEs within the CEM. It is assumed that the duration of each utility decrement lasts one month. The treatment-related AE decrements and duration estimates are presented in Table 66.

**Table 66: Utility decrements and duration by treatment-related AE**

| Treatment-related AE | Disutilities | Source | Duration of event (months) | Source |
|---|---|---|---|---|
| Decreased platelets count | 0.0000 | *Assumption – these are laboratory results which are managed through dose modifications* | 1 | *Assumption* |
| Thrombocytopenia | 0.0000 | | 1 | *Assumption* |
| Increased blood triglyceride concentration | 0.0000 | | 1 | *Assumption* |
| Hyperglyceridaemia | 0.0000 | | 1 | *Assumption* |
| Diarrhoea | -0.0470 | *Vamorolone NICE submission; Sullivan et al. 2011*[130, 225] | 1 | *Assumption* |
| Abdominal pain | -0.0470 | *Assumed the same as diarrhoea* | 1 | *Assumption* |
| Upper abdominal pain | -0.0470 | *Assumed the same as diarrhoea* | 1 | *Assumption* |
| Vomiting | -0.0950 | *Vamorolone NICE submission; Hagiwara et al. 2018*[226] | 1 | *Assumption* |

Abbreviations: QALY, quality adjusted life year; AE, adverse event.

### B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 69 presents the utilities applied in the CEM in the base case. For health state patient utilities, the values reported in Audhya et al. 2023 are applied as its measurements align with the health states specified in the CEM and the methods for determining utilities align with the NICE reference case i.e. the EQ-5D measure was used and self-reported by patients.[95] This study is also the most recent patient HRQoL data available in DMD. Where required, the


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health states reported in Audhya et al. 2023 have been mapped to the health states in the CEM (see footnotes in Table 69). Where health states reported in Audhya et al. 2023 were thought to overlap with more than one health state in the CEM, a weighted average has been derived from the published utility values. Utility decrements applied to patient utilities for comorbidities and treatment-related AEs are sourced from the literature. Scenario analyses explore the use of the patient health state utilities reported in Landfeldt et al. 2017 and the BOI study.[192, 193]

The CEM includes caregiver HRQoL (Section B.1.3.1 and Section B.3.2.2). The base case includes caregiver HRQoL for two caregivers – aligning with feedback in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135).[130] The assumption of two caregivers may be conservative as feedback from patient advocacy groups heard during the second committee meeting for vamorolone emphasised how the impact of diagnosis and progression of DMD impacts the whole family network (e.g. siblings and grandparents) as well as requiring additional support from outside this network (e.g. schools). However, due to the uncertainty associated with estimating a precise number of caregivers, two are assumed in the base case. A scenario analysis explores the impact of three caregivers.

In the base case, the caregiver utilities are sourced from the UK caregiver vignette study (see Table 65).[98] A scenario analysis explores the caregiver utilities reported in Landfeldt et al. 2017.[192]

Four approaches to modelling caregiver HRQoL are considered as part of this appraisal: (1) caregiver utilities, (2) caregiver disutilities, (3) caregiver increments relative to the severe health state, and (4) caregiver increments relative to the midway health state. As discussed in Pennington et al. 2020; 2022a, two main methods have been used to incorporate caregiver HRQoL into NICE appraisals: (1) carer utilities and (2) carer disutilities.[227, 228] However, there is not a clear answer as to which approach is superior – reflected by the limited advice provided internationally from HTA bodies.[229] Across the five case studies detailed in Pennington et al. 2022b, the carer disutilities approach was the most used. This aligns with the findings from a review of HSTs by the EAG in the Evidence Assessment Report in the ataluren NICE appraisal.[7] During the NICE Decision Problem meeting for this appraisal, the EAG highlighted a third method (caregiver increments) which was used in NICE TA754.[230]

The challenges with how to incorporate caregiver HRQoL in economic evaluations is widely discussed in the literature, with the term of the ‘carer QALY trap’ coined.[231–234] The ‘carer QALY trap’ emerges when the intervention leads to survival gains where the HRQoL of the patient is low which can cause caregivers to lose QALYs, leading to an overall negative loss in QALYs from the extension in life. In this scenario, strictly maximizing QALYs introduces a trade-off between extending the life of the patient and reducing the burden of the caregiver. The HRQoL of a caregiver is assumed to be improved following the death of a patient compared to the HRQoL experienced through an extension in life for the patient. Put differently, it assumes that caregivers would be better off—in terms of HRQoL—grieving the premature death of their son as opposed to caring for him.

As givinostat indirectly improves survival, through reducing the speed of progression, the ‘carer QALY trap’ is relevant to this appraisal. Negative caregiver QALYs arising from extended survival has been viewed as perverse by patient experts in previously published


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NICE appraisals in DMD and other disease areas; if caregivers prefer the extension in life with low patient HRQoL health states over death, then negative QALYs should not be possible.[235, 236] Following this feedback, the approaches explored in this submission anchor caregiver HRQoL based on a cure being the best possible outcome for the caregivers and patient death being the worst possible outcome for the caregivers. This assumption avoids the challenges associated with the 'carer QALY trap' and is supported by feedback in previous NICE submissions. Based on this assumption, the four approaches to modelling caregiver HRQoL result in the same impact on the ICER. Therefore, this assumption comes with the added benefit of reducing the uncertainty stemming from alternative approaches to modelling caregiver HRQoL. The caregiver increments relative to the midway health state is applied in the base case; alternative approaches are presented in the scenario analyses and are shown to have no impact.

The caregiver increments relative to the midway health state estimates utility increments or decrements relative to the midway health state i.e., health state (4) 'HTMF, no ventilation' using the utility values from the UK caregiver vignette study in the base case and applies these to the additional time spent in the respective health states compared to ECM. Table 67 details how these utility increments and decrements are derived from the values sourced from the UK caregiver vignette study. This results in caregiver increments being applied for extensions in health states (1-3) i.e., the ambulatory health states and caregiver decrements being applied for extensions in health states (5-8) i.e., the non-ambulatory health states and death.

**Table 67: Calculation of utility increments and decrements in the caregiver increments relative to the midway health state approach to modelling caregiver utilities**

| Health states | Utilities | Increments/decrements: relative to midway |
|---|---|---|
| 1 - Early ambulatory | 0.720 | 0.160 (0.720 – 0.560) |
| 2 - Late ambulatory | 0.670 | 0.110 (0.670 – 0.560) |
| 3 - Transfer | 0.580 | 0.020 (0.580 – 0.560) |
| 4 - HTMF, no ventilation | 0.560 | 0.000 (Anchor) |
| 5 - No HTMF, no ventilation | 0.500 | -0.060 (0.500 – 0.560) |
| 6 - HTMF, night-time ventilation | 0.540 | -0.020 (0.540 – 0.560) |
| 7 - No HTMF, night-time ventilation | 0.510 | -0.050 (0.510 – 0.560) |
| 8 - Full time ventilation | 0.480 | -0.080 (0.480 – 0.560) |
| 9 - Death (bereavement - all deaths) | 0.000 | -0.560 (0.000 – 0.560) |

Abbreviations: HTMF, hand to mouth function.


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With the caregiver increments relative to the midway health state approach, no caregiver QALYs are accrued in the ECM arm. In the givinostat arm, this approach multiplies the utility increments or decrements by the difference in LYs accrued from treatment with givinostat compared to ECM. In Table 68, caregiver LYs are presented for two caregivers across all the health states included within the CEM for ECM and givinostat. Treatment with givinostat is shown to increase the caregiver LYs in all health states except for health state (8) and death compared to ECM – aligning with the patient outcomes presented in Table 60. The incremental caregiver LYs are then multiplied by the respective caregiver increments or decrements (Table 67) to estimate the caregiver QALY impact from treatment with givinostat relative to ECM. This results in a QALY gain applied to givinostat for health states (1-3), health state (8), and death and a QALY loss applied to givinostat for health states (5-7).

The QALY gains in health states (1-3), health state (8), and death align with expectations as givinostat is anticipated to increase the time spent in the ambulatory health states vs. ECM, which is associated with an improved caregiver HRQoL. Givinostat is shown to reduce the time spent in the final health state (8) vs. ECM, which is associated with a low caregiver HRQoL. Therefore, reducing time in this final health state has a positive impact on caregiver QALYs. Additionally, givinostat is shown to extend survival of the patient i.e., reduce time in the death health state. Assuming that patient death is the worst possible outcome for caregiver HRQoL, increasing survival has a positive impact on caregiver QALYs. The QALY loss in health states (5-7) also aligns with expectations as givinostat is anticipated to increase the time spent in these health states vs. ECM, which is associated with a low caregiver HRQoL. In summary, the approach to modelling caregiver utilities results in clinically plausible QALY gains and losses which are anticipated from treatment with givinostat compared to ECM.


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**Table 68: Calculation of caregiver QALY impact in the caregiver increments relative to the midway health state approach to modelling caregiver utilities**

| | **Health states** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **Death** |
| Caregiver LYs in ECM | 7.81 | 4.50 | 2.05 | 3.53 | 4.78 | 4.58 | 3.78 | 11.14 | 97.83 |
| Caregiver LYs in givinostat | 13.04 | 7.44 | 3.35 | 11.63 | 13.31 | 8.22 | 6.08 | 8.08 | 68.86 |
| **Incremental caregiver LYs** | **5.22** | **2.94** | **1.30** | **8.10** | **8.53** | **3.64** | **2.30** | **-3.06** | **-28.97** |
| Caregiver increments/decrements | 0.16 | 0.11 | 0.02 | 0.00 | -0.06 | -0.02 | -0.05 | -0.08 | -0.56 |
| **Caregiver QALYs applied in ECM arm** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** |
| **Caregiver QALYs applied in givinostat arm** | **0.84** | **0.32** | **0.03** | **0.00** | **-0.51** | **-0.07** | **-0.12** | **0.25** | **16.22** |

Abbreviations: ECM, established clinical management; LY, life year; QALY, quality adjusted life year.


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**Table 69: Summary of utility values for cost-effectiveness analysis**

| State | Utility value: mean (standard error) | 95% confidence interval | Reference in submission (section and page number) | Justification |
|---|---|---|---|---|
| **Patient utilities** | | | | |
| Early ambulatory | 0.79 (0.06) | 0.66, 0.89 | Section B.3.4.3, page 175 | Patient utilities are sourced from Audhya et al. 2023.[95] This study reports patient-reported EQ-5D values (aligning with the NICE preferred measurement), considers an extensive range of clinical and functional health states, and reflects recent data (published in 2023). |
| Late ambulatory | 0.64 (0.11) | 0.42, 0.83 | Section B.3.4.3, page 175 | |
| Transfer | 0.64 (0.11) | 0.42, 0.83 | Section B.3.4.3, page 175 | |
| HTMF, no ventilation | 0.28 (0.02)a | 0.24, 0.32 | Section B.3.4.3, page 175 | |
| HTMF, night ventilation | 0.25 (0.06) | 0.14, 0.38 | Section B.3.4.3, page 175 | |
| No HTMF, no ventilation | 0.26 (0.03) | 0.21, 0.31 | Section B.3.4.3, page 175 | |
| No HTMF, night ventilation | 0.14 (0.09)b | 0.02, 0.36 | Section B.3.4.3, page 175 | |
| Full ventilation | 0.14 (0.09)b | 0.02, 0.36 | Section B.3.4.3, page 175 | |
| Spinal fusion surgery | -0.070 (0.0070) | -0.0569, -0.0843 | Section B.3.4.4, page 181 | Treatment with givinostat will reduce the number of patients who require spinal fusion surgery beyond the impact reflected by the health state costs and utilities. Therefore, a utility decrement is applied to patients requiring spinal fusion surgery. |
| Decreased platelets count | 0.0000 (0.0000) | 0.0000, 0.0000 | Section B.3.4.5, page 181 | Utility decrements are included to reflect the differential HRQoL impact from treatment-related AEs. |
| Thrombocytopenia | 0.0000 (0.0000) | 0.0000, 0.0000 | Section B.3.4.5, page 181 | |
| Increased blood triglyceride concentration | 0.0000 (0.0000) | 0.0000, 0.0000 | Section B.3.4.5, page 181 | |
| Hyperglyceridaemia | 0.0000 (0.0000) | 0.0000, 0.0000 | Section B.3.4.5, page 181 | |
| Diarrhoea | -0.0470 (0.0047) | -0.0382, -0.0566 | Section B.3.4.5, page 181 | |
| Abdominal pain | -0.0470 (0.0047) | -0.0382, -0.0566 | Section B.3.4.5, page 181 | |
| Upper abdominal pain | -0.0470 (0.0047) | -0.0382, -0.0566 | Section B.3.4.5, page 181 | |
| Vomiting | -0.0950 (0.0095) | -0.0722, -0.1144 | Section B.3.4.5, page 181 | |


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| **Caregiver utilities (increments/decrements calculated from these in the base case)** | | | | |
|---|---|---|---|---|
| Early ambulatory | 0.72 (0.02) | 0.67, 0.77 | Section B.3.4.3, page 180 | Values are sourced from the UK caregiver vignette study which aligns with the granularity of the Project HERCULES NHM.[98] Modelling of caregiver utilities is based on the increments or decrements anchored to the midway health state approach to modelling caregiver utilities. This results in clinically plausibly QALY gains/losses for givinostat vs. ECM. |
| Late ambulatory | 0.67 (0.03) | 0.62, 0.72 | Section B.3.4.3, page 180 | |
| Transfer | 0.58 (0.03) | 0.52, 0.64 | Section B.3.4.3, page 180 | |
| HTMF, no ventilation | 0.56 (0.03) | 0.5, 0.62 | Section B.3.4.3, page 180 | |
| HTMF, night ventilation | 0.5 (0.03) | 0.43, 0.57 | Section B.3.4.3, page 180 | |
| No HTMF, no ventilation | 0.54 (0.03) | 0.48, 0.6 | Section B.3.4.3, page 180 | |
| No HTMF, night ventilation | 0.51 (0.03) | 0.45, 0.57 | Section B.3.4.3, page 180 | |
| Full ventilation | 0.48 (0.03) | 0.41, 0.55 | Section B.3.4.3, page 180 | |

[a]Weighted across preserved upper limb, no daytime ventilation, without symptomatic cardiomyopathy; mildly impaired upper limb, no daytime ventilation, without symptomatic cardiomyopathy; mildly impaired upper limb, no daytime ventilation, with symptomatic cardiomyopathy; moderately impaired upper limb, no daytime ventilation, without symptomatic cardiomyopathy; and moderately impaired upper limb, no daytime ventilation, with symptomatic cardiomyopathy; [b]Weighted across loss of upper limb function, nighttime, and daytime ventilation, without symptomatic cardiomyopathy and loss of upper limb function, nighttime, and daytime ventilation, with symptomatic cardiomyopathy.


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## *B.3.5 Cost and healthcare resource use identification, measurement and valuation*

Four broad categories of healthcare costs are included in the CEM, including therapy-related costs, health-state costs, comorbidity costs, and treatment-related AE costs.

Costs reflect the latest available source i.e. eMIT accessed June 2024, British National Formulary (BNF) accessed June 2024, NHS Reference Costs 2022/23, and the PSSRU 2023.[194, 195, 204, 237] Costs collected from other sources are inflated to 2022/23 using inflation indices in the PSSRU, where appropriate.

### B.3.5.1 Cost and health resource use studies

Cost and health resource use data have been identified from an SLR and the Project HERCULES UK BOI study (unpublished).[193, 238]

From these studies three sources of health state costs are included in the CEM: (1) the Project HERCULES UK CPRD study (Morgan et al. 2024; base case), (2) Landfeldt et al. 2017 which is informed by Landfeldt et al. 2014 – as identified in the cost and health resource use SLR (scenario analysis), and (3) the Project HERCUES UK BOI study (scenario analysis).[56, 192, 238] Table 70 compares each of the sources in terms of population and which resources are included. Table 71 compares the health state costs from each of the sources uplifted to 2022/23 using the inflation indices published in PSSRU 2023.[237]

Landfeldt et al. 2014; 2017 and the Project HERCULES UK BOI study include costs not funded by the NHS or PSS. To align with the NICE reference case and feedback from the EAG in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135), Table 71 shows only direct medical costs from Landfeldt et al. 2014; 2017 and only direct medical costs and home alterations from the Project HERCULES UK BOI study.[130] Note: treatment costs were removed from the Project HERCULES UK BOI results as these are considered separately in the CEM.


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**Table 70: A comparison of health-state specific costs and resource use studies**

| | Project HERCULES CPRD[238] | Landfeldt et al. 2014; Landfeldt et al. 2017[56, 192] | Project HERCULES BOI[193] |
|---|---|---|---|
| **Population** | Patients with muscular dystrophy. Patients were excluded if they were female, had a diagnosis of Becker's dystrophy anywhere in their patient record or were aged over 40 years during the study period. | Patients with DMD from the TREAT-NMD network, aged ≥5-years | Patients with DMD diagnosis at least 24 months before the index date |
| **N** | N=639 | N=770 | N=44 (total costs)<br>129 (direct medical costs)<br>44 (direct non-medical costs)<br>44 (indirect costs) |
| **Health states** | Ambulatory<br>Non-ambulatory, no ventilation<br>Non-ambulatory, ventilation | Early ambulatory<br>Late ambulatory<br>Early non-ambulatory<br>Late non-ambulatory | Early ambulatory<br>Late ambulatory<br>Transfer<br>HTMF, no ventilator<br>No HTMF, no ventilator<br>HTMF, night ventilator<br>No HTMF, night ventilator<br>Full ventilation |


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| | | | |
|---|---|---|---|
| **Costs and resource use included** | Primary care<br>Prescriptions<br>Outpatient appointments<br>A&E attendances<br>Inpatient admissions | Hospital admissions (including emergency and respite care)<br>Visits to physicians and other HCPs (including nurse, GP, specialist physician, psychologist/therapist, physiotherapist/occupational therapist, Care coordinator/care advisor, dentist, dietitian/nutritionist, and speech/language/swallowing therapist).<br>Tests and assessments<br>Medications<br>Non-medical community services (home help, personal assistants, nannies, and transportation services).<br>Aids, devices, and investments (including investments to and reconstructions of the home (e.g. adaptations for wheelchair accessibility).<br>Informal care<br>Productivity losses | Direct medical cost (tests and procedures, medical devices, surgery, CS treatment, non-CS treatment, consultations, and hospitalisations)<br>Direct non-medical costs (other adaptations (remortgaging, vehicle adaptation and bills), alternative therapy, transport, OTC medication, home alteration, and professional caregiver)<br>Indirect costs (informal care and work productivity costs) |

Abbreviations: CPRD, Clinical Practice Research Datalink; CS, corticosteroid; HCPs, health care professionals; HTMF, hand-to-mouth function; OTC, over the counter.


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**Table 71: A comparison of health-state specific costs and resource use studies inflated to 2022/23 values**

| Health states, N | Health states, description | Project HERCULES CPRD[238] | Landfeldt et al. 2014; Landfeldt et al. 2017[56, 192] | Project HERCULES BOI[193] |
|---|---|---|---|---|
| 1 | Early ambulatory | £3,236 | £12,928 | £5,592 |
| 2 | Late ambulatory | £3,236 | £13,558 | £3,097 |
| 3 | Transfer | £3,236 | | £3,592 |
| 4 | HTMF, no ventilation | £6,551 | £19,980 | £2,370 |
| 5 | No HTMF, no ventilation | £6,551 | | £3,349 |
| 6 | HTMF, night ventilation | £8,773 | | £8,430 |
| 7a, 7b | No HTMF, night ventilation | £8,773 | £33,429 | £7,978 |
| 8a, 8b | Full ventilation | £8,773 | | £10,506 |

Abbreviations: BOI, burden of illness; CPRD, Clinical Practice Research Datalink; HTMF, hand-to-mouth function.

In the base case, the CEM uses the health-state costs from the Project HERCULES CPRD study (Morgan et al. 2024). These data reflect a large cohort (639 patients), are UK-specific, represent the most recent data and align with the NICE reference case i.e. costs relate to NHS and PSS resources and are valued using the prices relevant to the NHS and PSS. Additionally, the costs are shown to increase as the disease progresses across the health states, which aligns with expectations in UK clinical practice.

Although the values reported in Landfeldt et al. 2014; 2017 are supportive of the outcomes from the Project HERCULES UK CPRD study – costs are shown to increase across the progressing health states - these values are not considered within the base case as costs do not exclusively reflect the UK setting. Landfeldt et al. 2014; 2017 consider data from Germany, Italy, UK, and US. Additionally, these data were collected in 2012-2013. Nevertheless, due to the case precedence of use of the Landfeldt et al. 2017 study in the ongoing and previous NICE appraisals in DMD (vamorolone [GID-TA11135] and ataluren [HST22]), the health state costs reported in this study are explored in a scenario analysis.[7, 130]

The health state costs from the Project HERCULES UK BOI study are also considered in a scenario analysis. The Project HERCULES UK BOI study does not inform the base case due to low patient numbers, which may be driving the lack of validity from results i.e. costs do not necessarily increase with progression. Additional feedback from the Project HERCULES authors indicated limitations relating to difficulties in sampling which meant different health states were not adequately reflected, the 12-month recall period was considered limiting as many costs associated with DMD occur during transition periods between health states


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rather than being evenly spread across the time spent in each health state, and the burden for later health states was considered to be poorly characterised.

**Cost and health resource use SLR**

An SLR was conducted to identify relevant published evidence of the costs and healthcare resource use of DMD. Searches were conducted through May and June 2024, and updated in November 2024. The methodology undertaken is described in Appendix I, which details the search strategy, eligibility criteria applied, and full list of identified references. A total of 21 publications were included in the cost and resource use SLR from the database searches, grey literature searches, and hand searching.

Appendix I details the 21 identified publications. Of the 21 publications, five reported outcomes from a UK perspective using Great Britain pounds as the currency (Morgan et al. 2024, the ataluren submission to NICE, the ataluren submission to SMC, Hind et al. 2017, and Landfeldt et al. 2017).[7, 123, 192, 238, 239] The ataluren submission to NICE and the SMC cite Landfeldt et al. 2017 for health state resource use costs. Therefore, the main body of this submission dossier summarises the cost and health resource use data in patients with DMD from Hind et al. 2017 and Landfeldt et al. 2017 only.

Morgan et al. 2024 report on an epidemiology and healthcare resource utilisation study which has been conducted using the UK CPRD dataset as part of Project HERCULES.[238] Patients with DMD were selected by medical codes from the Clinical Practice Research Datalink Aurum database and matched to non-DMD controls.

Patients were followed from resource index date which was the latter of the 01 April 2007 or the patient's registration date until resource end date which the earliest of a patients end of follow-up date 30 June 2019. Primary care, inpatient, outpatient and A&E department contacts and prescriptions emanating from primary care were aggregated and their costs compared between cases and controls. DMD patients were further classified by ambulatory phase and ventilation status and respective costs presented.

240 patients with DMD were registered at a CPRD Aurum practice on the midpoint of 2020: a point prevalence of 3.23 (95% CI 2.82-3.63) per 100,0000 in the general population and 6.43 (95% CI 5.61-7.24) per 100,0000 for the male population. This was equivalent to one DMD case per 30,992 population.

There was a significant increase in contacts in all healthcare sectors compared to controls: primary care (incidence rate ratios (IRR) =3.19 (95% CI 3.11-3.28)), inpatient admissions (IRR =9.24 (95% CI 8.19-10.46)), outpatient appointments (IRR =11.44 (95% CI 10.95-11.96)) and accident and emergency (IRR =1.65 (1.52-1.81)).

387 patients contributed data in the ambulatory phase, 188 in the non-ambulatory without ventilation phase and 64 in the non-ambulatory with ventilation phase. Total costs per annum (2019/20 costs) were £2,931 in the ambulatory phase, £5,938 in the non-ambulatory without ventilation and £8,748 in the non-ambulatory with ventilation phase (Table 72). Overall healthcare costs were almost ten-fold higher (adjusted cost ratio (CR) = 9.33 [95% CI 6.75-12.91]) compared with controls.


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**Table 72: Health state costs reported in the CPRD study in 2019/20 Great British Pounds**

| | Ambulatory | Non-ambulatory/no ventilation | Non-ambulatory/with ventilation |
|---|---|---|---|
| Patients, N | 387 | 188 | 64 |
| Follow-up (years) | 1591.3 | 678.8 | 199.7 |
| Cost per annum | | | |
| Primary care contacts | £176 | £274 | £429 |
| Prescriptions | £460 | £1,139 | £3,582 |
| Outpatient appointments | £1,398 | £1,212 | £1,083 |
| A&E attendances | £55 | £91 | £123 |
| Inpatient admissions | £841 | £3,221 | £3,531 |
| Total costs | £2,931 | £5,938 | £8,748 |

Abbreviations: A&E, accident and emergency; CPRD, Clinical Practice Research Datalink.

Whilst the CPRD encompasses both primary and secondary health care sources, there are certain data gaps and limitations that were acknowledged as part of the study:

- Diagnosis data is available in the primary care and inpatient datasets but within the version of the ICD-10 database used in the UK there is no specific code for DMD.
- The attribution of ambulatory status for three-quarters of patients was reliant upon a code for wheelchair use being recorded in the HES admitted patient care data. This necessitated the patient being admitted as inpatient and there may have been a considerable lag between the date the patient started using a wheelchair to the date the patient was admitted and had that diagnosis recorded. Similar considerations apply to the classification of ventilation status.
- Standard costing tariffs were applied in this study. The system does not discriminate for the complexity of a patient in the outpatient or accident and emergency settings.
- There are known limitations of the accident and emergency dataset in terms of coverage and missing data, particularly prior to 2016.

Hind et al. 2017 reported on a pilot randomised trial comparing aquatic therapy with land-based exercises in boys with DMD. Over 6 months, the estimated direct NHS costs ranged from £1,970 to £2,734 and the societal costs ranged from £2,541 to £3,775, based on attendance. Financial pressures and opportunity costs were noted by the physiotherapists as making the service difficult to justify.

Landfeldt et al. 2017)report health state costs informing their published CEM based on costs attained from their previously published cross-sectional, observational study (Landfeldt et al. 2014).[56] The authors estimated annual costs of DMD comprising direct medical costs, direct non-medical costs, informal care costs (i.e. paid and unpaid informal care by the primary caregiver) and indirect costs (i.e. production losses for the patient and primary caregiver due to absenteeism and impaired productivity while working). Direct medical costs included: hospital admissions, emergency care, respite care, visits to physicians and other healthcare practitioners (i.e. nurses, general practitioners, specialist physicians, psychologists,


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therapists, physiotherapists, occupational therapists, care coordinators/care advisors, dentists, dietitians/nutritionists and speech/language/swallowing therapists), tests and assessments, medications, medical aids, devices and investments, and community services (e.g. home help and personal assistants). Direct non-medical costs included: aids, devices, and investments.

Data on healthcare resource use were collected through an online questionnaire completed by patients with DMD and a caregiver – participants were identified from Germany, Italy, United Kingdom, and United States through the Translational Research in Europe–Assessment & Treatment of Neuromuscular Diseases registries. A total of 770 patients (173 German, 122 Italian, 191 from the United Kingdom, and 284 from the United States) completed the questionnaire. The original paper (Landfeldt et al. 2014) presents costs in 2012 US dollars. Table 73 presents the healthcare costs reported in Landfeldt et al. 2017 in 2015 Great British Pounds. Costs are shown to increase with the stages of progression across all three categories of health state classification i.e. health states defined by DMDSAT, ambulatory status, and ventilation status.

**Table 73: Health state costs reported in Landfeldt et al. 2017 in 2015 Great British Pounds[192]**

| | Direct costs | | Indirect costs | | Total cost |
|---|---|---|---|---|---|
| | **Medical** | **Non-medical** | **Patient** | **Caregiver** | |
| **Model I (DMDSAT)** | | | | | |
| **Initial score** | £8,340 | £9,120 | £14,230 | £6,360 | £23,870 |
| **Per lost score (multiplier)** | 1.057 | 1.04 | NA | 1.037 | 1.053 |
| **Model II (ambulatory status)** | | | | | |
| **Early ambulatory** | £10,670 | £9,740 | £0 | £7,180 | £27,590 |
| **Late ambulatory** | £11,190 | £11,420 | £0 | £8,340 | £30,950 |
| **Early non-ambulatory** | £16,490 | £17,860 | £0 | £12,810 | £47,160 |
| **Late non-ambulatory** | £27,590 | £16,810 | £14,230 | £11,240 | £66,720 |
| **Model III (ventilation status)** | | | | | |
| **None** | £11,520 | £12,660 | £14,230 | £9,160 | £34,520 |
| **Night-time** | £31,710 | £14,610 | £14,230 | £10,490 | £61,490 |
| **Day and night-time** | £36,390 | £15,500 | £14,230 | £12,860 | £83,250 |

Abbreviations: DMDSAT, Duchenne muscular dystrophy Functional Ability Self-Assessment Tool.

### Project HERCULES UK BOI study

In addition to the SLR, as described above, a BOI study has been conducted as part of Project HERCULES.[193] The BOI study collected costs, resource use, and HRQoL data from neuromuscular specialists, patients, and caregivers in the UK.


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Specific to healthcare resource use, data were collected through CRFs completed by neuromuscular specialists and PPIEs completed by patients and/or caregivers. CRFs collected data relating to hospitalisations (day case, outpatient, inpatient, length of stay), surgical procedures (number and type of surgeries, length of stay, time spent in intensive care), consultant visits (physicians, nurses, primary care, and specialities), tests and examinations (respiratory tests, blood tests, serum tests, and diagnostic imaging), and treatments (frequency and dose). PPIEs collected data relating to direct non-medical and indirect costs. Direct non-medical costs reflected the requirement for aids or equipment, professional caregivers, alternative therapies (over the counter medications, alternative and holistic therapies, exercise, physiotherapy, and other DMD related costs), transportation costs, and transfer payments. Indirect costs reflected the work productivity impact in patients and caregivers. Resource use data were aggregated and stratified by health state (based on the NHM). Following this, unit costs, sourced from eMIT, the NHS Reference Costs 2018/19, and the BNF, were used to estimate total costs.

Table 74 presents the total direct medical, direct non-medial, and indirect costs accrued over the course of 12-months from the BOI study. Table 75 provides the disaggregated direct medical costs – the categories with the highest costs were non-CS therapy and medical devices. Table 76 provides the disaggregated direct non-medical costs and indirect costs - use of a professional caregiver was the highest overall non-direct medical cost.


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**Table 74: Total direct medical, direct non-medical, and indirect costs from UK BOI study (2018/19 cost year)[193]**

| Health state | 1 | 2 | 3 | 4 | 5 | 6 | 7a, 7b | 8a, 8b | Overall |
|---|---|---|---|---|---|---|---|---|---|
| **Physician reported (n)** | 15 | 2 | 3 | 3 | 8 | 5 | 4 | 4 | 44 |
| ***Direct medical cost, mean (SD)*** | £5425.88 (4904.22) | £5034.12 (6059.3) | £3030.91 (3823.81) | £2990.38 (3213.41) | £3559.92 (4888.49) | £5909.92 (3069.56) | £6452.29 (2647.74) | £9676.29 (1100.39) | £5274.17 (4293.76) |
| **Patient reported (n)** | 15 | 2 | 3 | 3 | 8 | 5 | 4 | 4 | 44 |
| ***Direct non-medical cost, mean (SD)*** | £4614.29 (8828.35) | £642 (603.87) | £475 (173.85) | £579.67 (374.86) | £519.38 (134.35) | £241 (212.85) | £580.25 (105.01) | £3005.25 (4331.59) | £2121.92 (5524.13) |
| ***Indirect cost, mean (SD)*** | £6337.5 (7281.23) | £0 (0) | £15210 (17425.24) | £33208.5 (12317.6) | £38690.44 (4834.46) | £38177.1 (8842.75) | £40496.63 (6611.69) | £17491.5 (25100.34) | £22106.35 (18236.07) |
| **Total Cost (n)** | 15 | 2 | 3 | 3 | 8 | 5 | 4 | 4 | 44 |
| **Mean (SD)** | £16377.67 (14791.23) | £5676.12 (6663.17) | £18715.91 (17515.49) | £36778.54 (8741.53) | £42769.73 (6740.5) | £44328.02 (10829.17) | £47529.17 (6371.05) | £30173.04 (24289.04) | £29502.44 (18419.19) |

Abbreviations: BOI, burden of illness; N, number; SD, standard deviation.


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**Table 75: Disaggregation of direct medical costs yielded from CRFs collected in the UK BOI study (2018/19 cost year)[193]**

| Health states | 1 | 2 | 3 | 4 | 5 | 6 | 7a, 7b | 8a, 8b | Overall |
|---|---|---|---|---|---|---|---|---|---|
| **Direct medical cost, mean (SD)** | £30165.3 (95810.56) | £2719.25 (3027.8) | £84610.54 (183108.4) | £1974.19 (2093) | £2983.72 (3900.22) | £12285.29 (19323.97) | £7053.37 (3111.57) | £12817.46 (13446.55) | £18358.31 (69400.74) |
| **Health system (n)** | **40** | **20** | **7** | **7** | **14** | **16** | **10** | **15** | **129** |
| *Procedure/Test, mean (SD)* | £2507.45 (3361.88) | £1338.66 (2368.17) | £712.37 (1138.72) | £275.54 (348.8) | £1873.22 (3883.86) | £1586.29 (3078.99) | £1323.73 (1892.67) | £1588.79 (2662.45) | £1726.06 (2901.37) |
| *CS Tx, mean (SD)* | £115.79 (172.85) | £51.25 (134.09) | £88.68 (113.88) | £118.72 (111.65) | £81.41 (109.6) | £164.28 (202.81) | £121.09 (134.94) | £141.53 (165.35) | £111.13 (159.34) |
| *Non-CS Tx, mean (SD)* | £25347.07 (96733.87) | £35.68 (43.46) | £81496.18 (183689.3) | £46.76 (60.06) | £35.02 (49.44) | £4793.37 (18442.7) | £8.04 (10.62) | £3534.01 (13303.59) | £13299.78 (69871.42) |
| *Medical device, mean (SD)* | £1012.91 (1903.83) | £347.77 (1118.75) | £1288.04 (2199.75) | £647.51 (1705.98) | £77.48 (289.92) | £4885.59 (2194.22) | £5048.39 (2650.9) | £6670.12 (2378.36) | £2254.35 (2976.48) |
| *Consultation, mean (SD)* | £1145.33 (936.07) | £939.43 (548.18) | £1025.27 (343.67) | £885.66 (178.32) | £916.58 (285.36) | £855.76 (297.75) | £552.13 (315.71) | £883 (542.22) | £955.57 (634.83) |
| *Hospitalisation, mean (SD)* | £0 (0) | £6.46 (28.9) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £1 (11.38) |
| *Surgery, mean (SD)* | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) |

Abbreviations: BOI, burden of illness; CRF, case record form; CS, corticosteroid; N, number; SD, standard deviation; Tx, treatment.


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**Table 76: Disaggregation of direct non-medical costs yielded from PPIEs collected in the UK BOI study (2018/19 cost year)[193]**

| Health state | 1 | 2 | 3 | 4 | 5 | 6 | 7a, 7b | 8a, 8b | Overall |
|---|---|---|---|---|---|---|---|---|---|
| **Direct non-medical cost (n)** | **15** | **2** | **3** | **3** | **8** | **5** | **4** | **4** | **44** |
| *Mean (SD)* | £4614.29 (8828.35) | £642 (603.87) | £475 (173.85) | £579.67 (374.86) | £519.38 (134.35) | £241 (212.85) | £580.25 (105.01) | £3005.25 (4331.59) | £2121.92 (5524.13) |
| **Indirect cost (n)** | **15** | **2** | **3** | **3** | **8** | **5** | **4** | **4** | **44** |
| *Mean (SD)* | £6337.5 (7281.23) | £0 (0) | £15210 (17425.24) | £33208.5 (12317.6) | £38690.44 (4834.46) | £38177.1 (8842.75) | £40496.63 (6611.69) | £17491.5 (25100.34) | £22106.35 (18236.07) |
| **Direct non-medical itemised (n)** | **15** | **2** | **3** | **3** | **8** | **5** | **4** | **4** | **44** |
| Professional caregiver, mean (SD) | £1864.29 (6655.65) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £635.55 (3901.49) |
| Home alteration, mean (SD) | £163.33 (262.18) | £62.5 (88.39) | £100 (86.6) | £253.33 (387.99) | £46.88 (93.31) | £8 (17.89) | £17.5 (21.79) | £0.25 (0.5) | £93.66 (193.71) |
| OTC medication, mean (SD) | £52.67 (83.45) | £222 (31.11) | £31.67 (30.14) | £20 (18.03) | £39.38 (14) | £22 (20.19) | £30 (23.8) | £550 (420.32) | £93.95 (194.1) |
| Transport, mean (SD) | £123.33 (134.78) | £0 (0) | £73.33 (94.52) | £100 (173.21) | £3 (8.49) | £35 (78.26) | £18.75 (37.5) | £2362.5 (4430.08) | £274.86 (1351.33) |
| Transfer payments, mean (SD) | £100.67 (187.56) | £250 (353.55) | £150 (259.81) | £206.33 (186.82) | £430.13 (104.78) | £176 (167.38) | £514 (111.58) | £92.5 (185) | £223.32 (223.87) |
| Alternative therapy, mean (SD) | £910 (1619.96) | £100 (141.42) | £120 (207.85) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £0 (0) | £322.95 (1020.05) |
| Other non-medical costs, mean (SD) | *£1400 (5151.98)* | *£7.5 (10.61)* | *£0 (0)* | *£0 (0)* | *£0 (0)* | *£0 (0)* | *£0 (0)* | *£0 (0)* | *£477.61 (3015.32)* |
| **Indirect itemised (n)** | **15** | **2** | **3** | **3** | **8** | **5** | **4** | **4** | **44** |
| Non-professional caregiver, mean (SD) | £6337.5 (7281.23) | £0 (0) | £5070 (5808.42) | £12928.5 (5323.5) | £8270.44 (4834.46) | £7757.1 (8842.75) | £10076.63 (6611.69) | £9886.5 (11683.02) | £7587.72 (7114.28) |
| Retire/Stop working, mean (SD) | £0 (0) | £0 (0) | £10140 (17563) | £20280 (17563) | £30420 (0) | £30420 (0) | £30420 (0) | £7605 (15210) | £14518.64 (15369.94) |

Abbreviations: BOI, burden of illness; N, number; OTC, over the counter; PPIEs, Patient and Public Involvement and Engagements; SD, standard deviation.


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### B.3.5.2 Intervention and comparators' costs and resource use

Drug acquisition costs are calculated based on drug dosage, pack size, strength, compliance, dose reductions, and drug costs.

**Givinostat**

As detailed in Section B.3.2.3, the dose of givinostat is weight-based and reflects the EPIDYS clinical trial. In EPIDYS, boys received a flexible dose givinostat regimen, aimed at maximising efficacy, and starting with a high dose that was reduced if treatment was not tolerated. The protocol was amended to lower the starting dose, but the post hoc analysis of covariance (ANCOVA) suggested that the treatment effect was not affected by the change in treatment regimen (see Section B.2.6.1). In UK clinical practice, the dose of givinostat will vary based on compliance and dose modifications – as observed in the EPIDYS clinical trial.

In EPIDYS, compliance ([total number of expected doses - the total number of missed doses]/ total number of expected doses), was high in the givinostat treatment arm (98.3%). This was maintained in the OLE study where compliance was 98.6% across all patients. In the base case, the CEM applies the weighted rate from the EPIDYS and OLE data to all patients receiving treatment with givinostat to reflect the impact of compliance on the dose. A scenario analysis considers the impact of using data from EPIDYS only.

In EPIDYS, dose modifications were observed in 72.9% (86/118) of patients in the givinostat arm; dose reductions were the most reported type of modification reported in 48.3% (57/118) of patients. Other dose modifications included dose increased (6/118), dose permanently stopped (10/118), dose temporarily stopped (19/118), and dose skipped (47/118). In the OLE study, dose modifications were observed in 89.4% (185/207) across all patients; dose increases were the most reported type of modification reported in 70.0% (145/207) of patients. Other dose modifications included dose reduced (84/207), dose permanently stopped (21/207), dose temporarily stopped (69/207), and dose skipped (83/207).

The CEM reflects dose modifications using the distribution across the types of modification observed in the EPIDYS and OLE studies and the dose intensity relevant to each type as specified in the trial protocols:

- **Dose reductions:** In the trial protocols, dose reductions were allowed based on a 20.0% reduction from the permitted dose reduction regimen. Therefore, the CEM assumes 80.0% dose intensity for patients experiencing a dose reduction.

- **Dose temporarily stopped or skipped**: In the trial protocols, treatment could be resumed based on the permitted dose reduction regimen or a 20.0% reduction from this. Therefore, the CEM assumes 80.0% dose intensity for patients experiencing a dose temporarily stopped or skipped multiplied by actual treatment duration divided by the trial duration (to account for the number of days on which treatment was temporarily withdrawn or skipped). In EPIDYS the actual treatment duration was 488.5 days and the trial duration was 18 months. In the latest data cut from the OLE the actual treatment duration was 559.6 days and the median trial duration was 564.7 days. Therefore, the CEM assumes 71.3% (80.0% x 89.2%) and 79.3% (80.0% x 99.1%) dose intensity for patients resuming treatment after a dose temporarily stopped or dose skipped in the EPIDYS and OLE data, respectively.


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- **Dose increases:** Dose increases in EPIDYS and the OLE reflect weight gain. The CEM accounts for weight increase across the model time horizon on the dose of givinostat. Therefore, the CEM assumes 100.0% dose intensity for patients experiencing a dose increase.
- **Dose permanently stopped:** The CEM reflects permanent dose discontinuations using the discontinuation data from EPIDYS and the OLE – see Section B.3.3.4.

Table 77 presents the number of patients with and without dose modifications based on EPIDYS and the OLE and the assumed dose intensity for each dose modification. A scenario analysis considers the impact of using data from EPIDYS only.


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**Table 77: Givinostat dose intensity calculations**

| | EPIDYS | | OLE | | Weighted | Justification |
|---|---|---|---|---|---|---|
| | n/N (%) | Dose intensity | n/N (%) | Dose intensity | | |
| **No dose modifications** | 32/118 (27.1%) | 100.0% | 22/207 (10.6%) | 100.0% | 100.0% | Assumption |
| **Dose modifications** | 86/118 (72.9%) | 78.2% | 185/207 (89.4%) | 88.0% | 84.4% | Based on a weighted average across all dose modification types |
| Dose reductions | 57/86 (41.0%) | 80.0% | 84/185 (45.4%) | 80.0% | 80.0% | Based on dose reductions of 20.0% specified by trial protocols |
| Dose temporarily stopped | 19/86 (13.7%) | 71.3% | 69/185 (37.3%) | 79.3% | 76.4% | Based on dose reductions of 20.0% specified by trial protocols multiplied by actual treatment duration divided by the trial duration.<br>• In EPIDYS, actual duration of givinostat was 488.5 days (16.0 months) across the 18-month trial period (89.2%; 16.0/18). For patients resuming treatment a dose reduction of 20.0% was specified (71.3% = 89.2% x 80.0%).<br>• In the OLE, actual duration of givinostat was 559.6 days across the 564.7 days trial period (99.1%; 559.6/564.7). For patients resuming treatment a dose reduction of 20.0% was specified (79.3% = 99.1% x 80.0%). |
| Dose skipped | 47/86 (33.8%) | 71.3% | 83/185 (44.9%) | 79.3% | 76.4% | |
| Dose increased | 6/86 (4.3%) | 100.0% | 145/185 (78.4%) | 100.0% | 100.0% | Assumption – impact reflected by weight increase over time in CEM (Section B.3.2.1) |
| Dose permanently stopped | 10/86 (7.2%) | 100.0% | 21/185 (11.4%) | 100.0% | 100.0% | Assumption – impact reflected by treatment discontinuation in CEM (Section B.3.3.4) |

Abbreviations: n, number; OLE, open-label extension.


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The anticipated list price (excluding VAT) for 140mL of givinostat is £13,846. A patient access scheme (PAS) is pending approval from National Health Service England (NHSE); a simple discount of [redacted] is applied to the cost of givinostat – this reduces the price to £[redacted] per bottle.

**Established clinical management**

As detailed in Section B.3.2.3, in the base case, ECM therapy comprises 20.5% prednisone administered as 0.75 mg/kg orally, and 79.5% deflazacort administered as 0.90mg/kg orally. As per EPIDYS, 82.1% are assumed to receive a daily schedule and 17.9% are assumed to receive an intermittent schedule reflecting 10-days on and 10-days off i.e., half the dose of those patients receiving the daily schedule. In UK clinical practice, the dose of CS will vary based on compliance and dose modifications – as observed in the EPIDYS clinical trial.

In EPIDYS, compliance ([total number of expected doses - the total number of missed doses]/ total number of expected doses), was high in the placebo treatment arm (98.1%). The CEM applies this rate to all patients receiving treatment with CS to reflect the impact of compliance on the dose.

In EPIDYS, dose modifications were observed in 45.9% (28/61) of patients in the placebo arm; doses skipped were the most reported type of modification reported in 39.3% (24/61) of patients. Other dose modifications included dose increased (6/61), dose permanently stopped (1/61), dose temporarily stopped (6/61), and dose reduced (7/61). Table 78 presents the number of patients with and without dose modifications and the assumed dose intensity for each dose modification.

The CEM reflects dose modifications using the distribution across the types of modification observed in EPIDYS and the dose intensity aligning with the givinostat assumptions:

- **Dose reductions:** In line with the givinostat assumptions, the CEM assumes 80% dose intensity for patients experiencing a dose reduction.
- **Dose temporarily stopped or skipped**: In line with the givinostat assumptions, the CEM assumes the 80.0% dose intensity is multiplied by actual treatment duration in EPIDYS (502.7 days; 16.5-months) divided by the 18-month trial duration (91.7%), to account for the number of days on which treatment was temporarily withdrawn or skipped. Therefore, the CEM assumes 73.4% dose intensity for patients resuming treatment after a dose temporarily stopped or dose skipped.
- **Dose increases:** In line with the givinostat assumptions, the CEM assumes 100.0% dose intensity for patients experiencing a dose increase.
- **Dose permanently stopped:** The CEM reflects permanent dose discontinuations using the discontinuation data from EPIDYS – see Section B.3.3.4.

Table 78 presents the number of patients with and without dose modifications and the assumed dose intensity for each dose modification.


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**Table 78: CS dose intensity calculations**

| | EPIDYS n/N (%) | Dose intensity | Justification |
|---|---|---|---|
| **No dose modifications** | 33/61 (54.1%) | 100.0% | Assumption |
| **Dose modifications** | 28/61 (45.9%) | 78.7% | Based on a weighted average across all dose modification types |
| Dose reductions | 7/28 (15.9%) | 80.0% | Aligned with givinostat assumptions, dose reductions of 20.0% specified by trial protocols |
| Dose temporarily stopped | 6/28 (13.6%) | 73.4% | In EPIDYS, actual duration of CS was 502.7 days (16.5 months) across the 18-month trial period (91.7%; 16.5/18). For patients resuming treatment a dose reduction of 20.0% was specified (73.4% = 91.7% x 80.0%). |
| Dose skipped | 24/28 (54.5%) | 73.4% | |
| Dose increased | 6/28 (13.6%) | 100.0% | Assumption – impact reflected by weight increase over time in CEM (Section B.3.2.1) |
| Dose permanently stopped | 1/28 (2.3%) | 100.0% | Assumption – impact reflected by discontinuation data in CEM (Section B.3.3.4) |

Abbreviations: n, number; CS, corticosteroids.

Table 79 presents the inputs informing acquisition costs. Table 80 presents the cost per monthly cycle. Givinostat and CS are oral therapies. Therefore, no administration costs are assumed.


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**Table 79: Drug acquisition cost inputs**

| Therapy | Proportion of patients | Dose schedule | Dose/day | Compliance | Dose intensity | Mg/ unit | Units/ pack | Price/ pack |
|---|---|---|---|---|---|---|---|---|
| **Intervention – givinostat in combination with CS** | | | | | | | | |
| Givinostat | 100.0% | Twice daily | 10kg ≤ and < 12.5kg: 26.6mg<br>12.5kg ≤ and < 20kg: 43.7mg<br>20kg ≤ and < 25kg: 54.9mg<br>25kg ≤ and < 30kg: 59.3mg<br>30kg ≤ and < 40kg: 54.5mg<br>40kg ≤ and < 50kg: 65.3mg<br>50kg ≤ and < 60kg: 73.4mg<br>60kg ≤ and < 70kg: 80mg<br>70kg ≤: 93.4mg | 98.5% | 87.0% | 8.86 | 140.0 | £13,846<br>£[redacted]<br>(including [redacted] PAS) |
| Prednisone | 20.5% | 82.1% daily<br>17.9% intermittent (10-days on, 10-days off) | 0.75mg/kg | 98.1% | 90.2% | 5.0<br>10.0 | 10.0<br>1.0 | £8.51<br>£55.08 |
| Deflazacort | 79.5% | 82.1% daily<br>17.9% intermittent (10-days on, 10-days off) | 0.90mg/kg | 98.1% | 90.2% | 6.0 | 60.0 | £15.82 |
| **Comparator – ECM** | | | | | | | | |
| Prednisone | 20.5% | 82.1% daily<br>17.9% intermittent (10-days on, 10-days off) | 0.75mg/kg | 98.1% | 90.2% | 5.0<br>10.0 | 10.0<br>1.0 | £8.51<br>£55.08 |
| Deflazacort | 79.5% | 82.1% daily<br>17.9% intermittent (10-days on, 10-days off) | 0.90mg/kg | 98.1% | 90.2% | 6.0 | 60.0 | £15.82 |
| Source | EPIDYS[22] | EPIDYS and Guglieri et al. 2022[240] | EPIDYS and BNF[194] | EPIDYS | EPIDYS | ITF and BNF | ITF and BNF | ITF and eMIT[204] |

Abbreviations: BNF, British National Formulary; CS, corticosteroids; eMIT, electronic marketing information tool; ITF, Italfarmaco; PAS, patient access scheme.


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**Table 80: Drug acquisition cost per cycle**

| | Cost per monthly cycle (£) |
|---|---|
| **Givinostat** | |
| 10kg ≤ and < 12.5kg | £7,746<br>£[redacted] (including [redacted]% PAS) |
| 12.5kg ≤ and < 20kg | £12,726<br>£[redacted] (including [redacted]% PAS) |
| 20kg ≤ and < 25kg | £16,001<br>£[redacted] (including [redacted]% PAS) |
| 25kg ≤ and < 30kg | £17,262<br>£[redacted] (including [redacted] % PAS) |
| 30kg ≤ and < 40kg | £15,864<br>£[redacted] (including [redacted]% PAS) |
| 40kg ≤ and < 50kg | £19,003<br>£[redacted] (including [redacted]% PAS) |
| 50kg ≤ and < 60kg | £21,375<br>£[redacted] (including [redacted]% PAS) |
| 60kg ≤ and < 70kg | £23,297<br>£[redacted] (including [redacted]% PAS) |
| 70kg ≤ | £27,199<br>£[redacted] (including [redacted]% PAS) |
| **ECM** | |
| Prednisone | £0.64/kg |
| Deflazacort | £0.77/kg |

Abbreviations: ECM, established clinical management; PAS, patient access scheme.

### B.3.5.3 Health-state unit costs and resource use

Health-state costs reflect the ongoing costs of disease management. Costs differ depending on the stage of the disease, and as the disease progresses, the costs increase to reflect the increased burden of disease. Health-state costs are the same across treatment arms; differences between treatment arms regarding health-state costs arise based on how quickly an individual progresses through the health states.

As described in Section B.3.5.1, in the base case, the CEM uses the health-state costs from the Project HERCULES UK CPRD study (Table 81). Scenario analyses explore the impact of using the values in Landfeldt et al. 2014; 2017 and the Project HERCULES BOI study.

**Table 81: Direct medical health-state costs applied in the CEM (base case)**

| Health states, N | Health states, description | Project HERCULES UK CPRD[238] | |
|---|---|---|---|
| | | Value (SE) | 95% Confidence interval |
| 1 | Early ambulatory | £3,298 (£660) | £2,134 - £4711 |
| 2 | Late ambulatory | £3,298 (£660) | £2,134 - £4711 |


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| | | | |
|---|---|---|---|
| 3 | Transfer | £3,298 (£660) | £2,134 - £4711 |
| 4 | HTMF, no ventilation | £6,681 (£1336) | £4,324 - £9543 |
| 5 | HTMF, night ventilation | £6,681 (£1336) | £4,324 - £9543 |
| 6 | No HTMF, no ventilation | £9,843 (£1969) | £6,370 - £14,059 |
| 7a, 7b | No HTMF, night ventilation | £9,843 (£1969) | £6,370 - £14,059 |
| 8a, 8b | Full ventilation | £9,843 (£1969) | £6,370 - £14,059 |

Abbreviations: CPRD, Clinical Practice Research Datalink; HTMF, hand-to-mouth function.

### B.3.5.4 Adverse reaction unit costs and resource use

Section B.3.3.6 describes the treatment-related AEs included in the CEM. The costs associated with treatment-related AEs are displayed in Table 82.

The cost per treatment-related AE is multiplied by the proportion of patients experiencing each treatment-related AE in each CEM cycle. The costs are then totaled to calculate the total cost of managing treatment-related AEs by the treatment arm.

**Table 82: Treatment-related AEs costs**

| Event | Costs (£) | | Source[194, 204] |
|---|---|---|---|
| | Value (SE) | 95% Confidence interval | |
| Decreased platelet count | £0.00 (£0.00) | £0.00 - £0.00 | Assumed managed through dose reduction |
| Thrombocytopenia | £0.00 (£0.00) | £0.00 - £0.00 | Assumed managed through dose reduction |
| Increased blood triglyceride concentration | £0.00 (£0.00) | £0.00 - £0.00 | Assumed managed through dose reduction |
| Hyperglyceridaemia | £0.00 (£0.00) | £0.00 - £0.00 | Assumed managed through dose reduction |
| Diarrhoea | £0.41 (£0.08) | £0.27 - £0.59 | BNF Guidance; Loperamide eMIT accessed May 2024 (DAD014 and DAK002) |
| Abdominal pain | £3.31 (£0.66) | £2.14 - £4.73 | BNF Guidance (antispasmodics); Alverine eMIT accessed May 2024 (DAB042 and DAB001) |
| Upper abdominal pain | £3.31 (£0.66) | £2.14 - £4.73 | BNF Guidance (antispasmodics); Alverine eMIT accessed May 2024 (DAB042 and DAB001) |
| Vomiting | £4.61 (£0.92) | £2.98 - £6.59 | BNF Guidance; Cyclizine eMIT accessed May 2024 (DDF016, DDF036, and DDF090) |

Abbreviations: BNF, British National Formulary; eMIT, electronic marketing information tool; AE, adverse event.


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### B.3.5.5 Miscellaneous unit costs and resource use

**Co-morbidities**

As discussed in Section B.3.3.5, the CEM reflects costs and utilities relating to spinal fusion surgery in addition to health state effects.

The cost implications from experiencing scoliosis are captured through spinal fusion surgery events. Resource use and costs relating to spinal surgery align with the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135) (Table 83); costs have been uplifted to reflect the 2022/23 cost year using the inflation indices in the PSSRU 2023.[130, 237] The cost includes one complex spinal reconstruction procedure and two supporting procedures to treat scoliosis or other spinal deformities and is applied as a one-off cost within the CEM.

**Table 83: Cost of spinal fusion surgery**

| Resource | Cost per unit (£)[130, 237] | | Units per patient |
|---|---|---|---|
| | Value (SE) | 95% Confidence interval | |
| **Complex Spinal Reconstructive Procedures** | £27,035 (£5,407) | £17,496 - £38,617 | 1 |
| **Scoliosis or Other Spinal Deformity** | £5,539 (£1,108) | £3,584 - £7,911 | 2 |
| **Total one-off cost** | | | £38,113 |

**Societal costs**

The base case in the CEM considers the NHS and PSS perspective – as per the NICE reference case. However, the economic burden of DMD surpasses only costs to the NHS and PSS, additional costs include professional and non-professional caregivers, over the counter medications, transport, transfer payments, alternative therapies, productivity losses, and other costs.

Landfeldt et al. 2014 and Landfeldt et al. 2017 – identified in the cost and health resource use SLR - report direct non-medical and indirect costs for the patient and caregiver.[56, 192] Similarly, direct non-medical and indirect costs are available from the Project HERCULES UK BOI study.[193] Table 84 presents these societal costs by health state; costs are uplifted to the 2022/23 cost year using the inflation indices published in PSSRU 2023. Note: home alterations recorded in the Project HERCULES UK BOI study are included in the direct medical costs (Table 71). Therefore, these have been removed here. Scenario analyses consider the inclusion of societal costs from Landfeldt et al. 2014; 2017 and the Project HERCULES UK BOI study.

In the scenarios including societal costs, indirect costs relevant to spinal fusion surgery are also included. The one-off indirect cost related to this surgery align with the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135) and have been uplifted to the 2022/23 cost year using the inflation indices in PSSRU 2023 (£24,802).[130, 237]


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**Table 84: Societal health-state costs applied in the CEM (scenario analyses)**

| Health states, N | Health states, description | Landfeldt et al. 2014; Landfeldt et al. 2017[56, 192] | Project HERCULES UK BOI study[193] |
|---|---|---|---|
| 1 | Early ambulatory | £20,501 | £12,398 |
| 2 | Late ambulatory | £23,942 | £666 |
| 3 | Transfer | | £17,911 |
| 4 | HTMF, no ventilation | £37,160 | £38,539 |
| 5 | HTMF, night ventilation | | £45,007 |
| 6 | No HTMF, no ventilation | | £44,142 |
| 7a, 7b | No HTMF, night ventilation | £33,986 | £47,186 |
| 8a, 8b | Full ventilation | | £23,555 |

## *B.3.6 Severity*

As per NICE TSD23, the absolute shortfall and proportional shortfall for patients relevant to this submission are 29.1 and 82.6%, respectively. Inputs for the patients relevant to this submission reflect the results in Section B.3.10 and inputs for the general population are based on the DSU calculator.[241] Table 85 presents the inputs and calculations of absolute shortfall and proportional shortfall.

Based on the QALY weightings for severity published in NICE TSD 23 (Table 86), givinostat meets the criteria for the severity modifier of 1.7 with an absolute QALY shortfall of at least 18.

**Table 85: Calculation of absolute shortfall and proportional shortfall**

| | **Patient population** |
|---|---|
| Age (years) | 6.0 |
| Proportion male | 100% |
| QALYs for ECM from CEM | 6.1 |
| | **General population** |
| Life expectancy | 73.2 |
| QALYs | 64.6 |
| Discounted QALYs | 35.3 |
| | **Severity calculations** |
| Absolute shortfall | 35.3 – 6.1 = 29.1 |
| Proportional shortfall | (35.3 – 6.1)/35.3 = 82.6% |

Abbreviations: CEM, cost-effectiveness model; ECM, established clinical management; QALY, quality adjusted life year.


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**Table 86: QALY weightings for severity[241]**

| QALY weight | Proportional QALY shortfall | Absolute QALY shortfall |
|---|---|---|
| 1 | Less than 0.85 | Less than 12 |
| x1.2 | 0.85 to 0.95 | 12 to 18 |
| x1.7 | At least 0.95 | At least 18 |

Abbreviations: QALY, quality adjusted life year.

## *B.3.7 Benefits not captured in the QALY calculation*

As described in Section B.3.4.6, the givinostat CEM includes caregiver utilities for two caregivers, aligning with feedback in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135).[45] This likely underestimates the substantial caregiver and wider societal impact from givinostat for the treatment of DMD; assuming that a DMD diagnosis only effects two caregivers in a family is likely to substantially underestimate the potential burden of this debilitating disease. About one-third of parents believe that DMD has a negative influence on the psychological well-being and social life of the unaffected siblings.[94] Siblings often run the risk of being “voiceless” and may feel invisible to parents focused on the complex needs of their child with DMD.[98,99] Grandparents and other informal caregivers are also negatively impacted due to the increased burden on the family, and an increased need for informal care for boys with DMD.

Additionally, societal costs are key components in evaluating the cost-effectiveness of treatments in DMD given the substantial burden faced by patients and carers. Many informal caregivers to patients with DMD terminate their employment or reduce their working hours to find the time needed to care for their children, and those who do continue to work have markedly impaired productivity with high levels of absenteeism.[45] Whilst a scenario explores a broader costing perspective and considers the impact of societal costs, these only reflect the estimated societal costs whilst a patient is alive. There are likely additional societal and healthcare costs following a patient’s death which are not captured within the analysis.

## *B.3.8 Uncertainty*

Assessing evidence related to rare disease areas such as DMD presents unique challenges. There are several factors to consider which impact the quality of evidence.

The clinical management of DMD is heterogenous and based on a continuous balance of the benefits with the side effects which is highly patient specific. This is reflected by the differences in CS dosing schedules and durations of treatment observed in clinical practice. Therefore, there are challenges with modelling a representative ECM arm. Nevertheless, the real-world evidence reflecting the experience of N=209 boys with DMD, used in the modelling, provides the most accurate representation of ECM in the UK.[178]

There are challenges with showing the relative effectiveness of givinostat over a lifetime horizon. Many key outcomes in DMD, such as HTMF, pulmonary outcomes and survival, manifest years into the future, often outside the typical timeframe of a clinical trial. The CEM conservatively assumes that the improvement observed in outcomes from the EPIDYS and OLE studies translate into improvements in longer-term outcomes which are not yet observed using the relationship described in the literature for ECM. This requires a reliance


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on surrogate relationships which may introduce uncertainty in the modelling. However, assuming the same relationship holds for givinostat as for ECM is conservative for two reasons:

- Firstly, improving the skeletal muscle integrity/function and delaying the loss of ambulation, as observed with givinostat in EPIDYS and the OLE study, may have an exaggerated impact on longer-term outcomes.
- Secondly, continued treatment with givinostat may lead to a treatment effect above and beyond what we would expect to see translating from delaying the loss of ambulation.

Nevertheless, the treatment effect of givinostat on these longer-term outcomes is unknown. Therefore, the CEM assumes that the relationships between age at loss of ambulation and the longer-term outcomes are the same for givinostat as those observed for ECM. This means that no treatment effect is assumed beyond age at loss of ambulation i.e., it is expected that the delay in loss of ambulation will translate to improved outcomes regardless of the ongoing givinostat treatment.

There are uncertainties relating to the measurement of HRQoL in children and young people with DMD. The challenges with collecting HRQoL data in children are demonstrated by the lack of clear recommendations in the NICE manual with regards to the measurement and approach to measurement. There are additional uncertainties relating to modelling HRQoL of caregivers – with no consensus in the literature nor in the NICE manual as to the preferred approach to this.

The uncertainty in the model results is explored through extensive one-way sensitivity analysis (OWSA), probabilistic sensitivity analysis (PSA), and scenario analyses. In the OWSA, each variable is systematically increased and decreased based on 95% confidence intervals or published ranges. In the absence of data, the higher and lower values are calculated based on a standard error of ±20% of the mean value. Scenario analyses are also performed to assess the impact of alternative assumptions and data sources which are not captured within the OWSA and PSA.

## *B.3.9 Summary of base-case analysis inputs and assumptions*

### B.3.9.1 Summary of base-case analysis inputs

A summary of the key parameters used in the CEM is presented in Table 51, Appendix M.7.2.

### B.3.9.2 Assumptions

The assumptions included in the CEM are presented in Table 87.

**Table 87: Summary of assumptions applied in the CEM**

| Parameter | Base case | Justification |
|---|---|---|
| **Model settings and structure** | | |
| **Starting age** | 6 years | Aligns with the patient population and the population included in the EPIDYS study |


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| | | |
|---|---|---|
| **Starting health state** | All patients start in the early ambulatory health state | This reflects the inclusion criteria in the EPIDYS clinical trial |
| **Model transitions** | The model structure assumes that DMD is progressive i.e. no backwards transitions were permitted | This aligns with the published NHM, is supported by the C-Path D-RSC data and by feedback from UK clinicians[191] |
| | It is assumed that patients can only move to the adjacent health state or death | This is supported by the granular cycle length (one month) and reduces the computational complexity in the Microsoft Excel-based CEM. Additionally, it aligns with the approach in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135)[130] |
| | The CEM assumes that the mortality rate varies only by health state and that givinostat does not directly impact mortality, mortality is impacted indirectly through delayed progression | This is a conservative assumption supported by the C-Path D-RSC data and by feedback from UK clinicians |
| **Updated NHM** | The CEM assumes the updates to the published NHM termed "Updated NHM (analysis 2)" – see Section B.3.3.1 | The published NHM has been updated to align with UK real-world data and UK clinical expert feedback. This is supported by the potential over-estimation of outcomes relating to the published NHM, discussed by Broomfield et al. 2024 and by the Committee in the first Committee meeting for the ongoing vamorolone NICE appraisal. Outcomes from the updated NHM (analysis 2) are shown to align with external data sources (published literature, unpublished UK real-world data, and UK clinical feedback). Therefore, this approach is considered externally valid and reflective of outcomes anticipated in UK clinical practice |
| **Intervention and comparator** | | |
| **Givinostat treatment continuation rule** | No explicit treatment continuation rule is assumed for givinostat | This is supported by feedback from UK clinicians who stated that the decision to continue treatment follows no consistent rule and is based on continuous reviews and discussions with other members of the multi-disciplinary teams, caregivers, and patients |
| **Givinostat transitions beyond discontinuation** | For patients who discontinue treatment with givinostat, the CEM assumes health state transitions remain the same as for patients continuing to receive givinostat | The evidence supporting these transitions is demonstrated by the correlations between improved earlier outcomes and improved later outcomes widely documented in the DMD literature |
| **Givinostat and CS use** | It is assumed that givinostat will not impact CS use | There is no evidence indicating that givinostat will impact CS use. The feedback from UK clinicians is that the two therapies have completely different |


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| | | |
|---|---|---|
| | | mechanisms of action. Therefore, these therapies would be used additively |
| **CS dosing schedule and distribution** | The distribution of CS (prednisone vs. deflazacort) is based on EPIDYS | This aligns with the clinical data underpinning the relative efficacy of givinostat vs. ECM. This is not anticipated to have a significant impact on cost-effectiveness results as CS are received in both treatment arms |
| **CS treatment continuation rule** | No explicit treatment continuation rule is assumed for CS | This is supported by feedback from UK clinicians who stated that the decision to continue treatment follows no consistent rule and is based on continuous reviews and discussions with other members of the multi-disciplinary teams, caregivers, and patients |
| **Treatment duration, compliance, and dose modification** | Data from EPIDYS and the OLE inform treatment duration, adverse events, compliance, and dose modifications | The weighted EPIDYS and OLE data make use of the totality of data for givinostat |
| **Adverse events and co-morbidities** | | |
| **Treatment-related AEs** | The proportion of treatment-related AEs weighted across EPIDYS and the OLE are applied to patients receiving treatment across the CEM time horizon | This is a conservative assumption as analyses of the EPIDYS and OLE data indicate that treatment-related AEs reduce after three months of treatment |
| **Long-term steroid burden** | Due to lack of data on the burden of long-term CS use, these side effects are not included in the CEM | As givinostat is not anticipated to change CS use in patients with DMD, the side effects relating to CS use would be similar in both arms. Therefore, this assumption is not anticipated to impact cost-effectiveness results |
| **Timing of spinal fusion surgery** | Spinal fusion surgery is assumed on average four years following loss of ambulation and patients are eligible for spinal surgery in the CEM from 15-25 years | Aligned with data presented in McDonald et al. 2018 and assumptions in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135)[209] |
| **Relative effect of givinostat on spinal fusion surgery** | The CEM assumes that the loss of ambulation HR for givinostat vs. ECM i.e., 0.51 is applied to the scoliosis surgery rate with ECM | No cases of scoliosis surgery were observed in patients treated with givinostat in EPIDYS or the OLE study. As reported in McDonald et al. 2018, scoliosis surgery is assumed on average four years following loss of ambulation. Therefore, the data from the givinostat studies may not be sufficiently mature to conclude on the relative reduction in scoliosis surgery. As a conservative approach, the CEM assumes that the loss of ambulation HR for givinostat vs. ECM i.e. 0.51 is applied to the scoliosis surgery rate with ECM. |
| **Utilities** | | |
| **Treatment-related AEs** | It is assumed that the duration of each utility decrement lasts one month | Treatment-related AEs are managed through dose modifications and specific treatment. Therefore, it is anticipated that the treatment-related AE will not last more than one month |


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| | | |
|---|---|---|
| **Number of caregivers** | Two | The assumption of two caregivers may be conservative as feedback from patient advocacy groups emphasises how the impact of diagnosis and progression of DMD impacts the whole family network (e.g. siblings and grandparents) as well as requiring additional support from outside this network (e.g. schools) |
| Abbreviations: AE, adverse events; DMD, Duchenne muscular dystrophy; ECM, established clinical management; OLE, open-label extension. | | |

## *B.3.10 Base-case results*

This Section presents the results from the CEM comparing givinostat to ECM in a population of people with DMD using both the PAS and list price for givinostat, respectively. A simple PAS of [redacted] is pending approval from NHSE; this is applied to the cost of givinostat and reduces the price to 59% per bottle.

Additionally, as shown in Section B.3.6, givinostat meets the criteria for a 1.7 severity modifier. This is applied to the incremental QALYs and is reflected in the ICERs presented in this Section.

### B.3.10.1 Base-case incremental cost-effectiveness analysis results

In the base case analysis and applying the PAS, givinostat accrues 22.4 additional QALYs (13.2 excluding the severity modifier) at an additional cost of £[redacted] per patient, resulting in an ICER of £[redacted] (Table 88).

Whilst givinostat is associated with greater total costs vs. ECM, givinostat is associated with cost savings in full-time ventilation costs ([redacted] per patient) and spinal fusion surgery costs ([redacted] per patient). These savings are driven by givinostat prolonging the time to reach full-time ventilation compared with ECM alone and a lower rate of scoliosis requiring spinal fusion surgery. The net health benefit (NHB) is [redacted] and the net monetary benefit (NMB) is [redacted], based on a willingness to pay (WTP) threshold of £30,000.

Appendix J presents predicted clinical outcomes and disaggregated results.

**Table 88: Base case results (with PAS)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc costs (£) | Inc LYG | Inc QALYs* | ICER (£/QALY)* |
|---|---|---|---|---|---|---|---|
| **Givinostat** | [redacted] | 21.9 | 19.3 | | | | |
| **ECM** | £99,448 | 14.6 | 6.1 | [redacted] | 7.3 | 22.4 | [redacted] |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.
*Including the 1.7 severity modifier

**Table 89: Base case results (list price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc costs (£) | Inc LYG | Inc QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|


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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Givinostat** | £3,272,344 | 21.9 | 19.3 | | | | |
| **ECM** | £99,448 | 14.6 | 6.1 | £3,172,896 | 7.3 | 22.4 | £141,583 |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; QALY, quality adjusted life year.

## *B.3.11 Sensitivity analyses*

### B.3.11.1 Probabilistic sensitivity analysis

The PSA explores the joint uncertainty of all relevant model parameters and their associated impact on cost-effectiveness results, by randomly varying all parameters within assigned distributions and then re-estimating and recording the ICERs at each random sample (referred to as an iteration). Parameters and their distributions and ranges used are presented in Appendix M.7.2. This is repeated for 1,000 iterations; the average ICER is reasonably stable after 1,000 iterations. The results of each PSA iteration are visually shown on a scatterplot of the incremental costs against the incremental QALYs. A cost-effectiveness acceptability curve (CEAC), corresponding to the PSA results, illustrates the probability that a treatment provides a cost-effective treatment option at varying WTP thresholds.

Including the PAS, the average incremental costs over the simulated results are [redacted] and the average incremental QALYs are 22.5 (including the severity modifier), giving a probabilistic ICER of [redacted]. This is congruent with the deterministic ICER of [redacted], as demonstrated by the overlap in markers showing the deterministic and probabilistic base case in the cost-effectiveness plane (Figure 52). The CEAC is depicted in Figure 52. The proportions of simulations considered cost-effective at a threshold of £30,000 and £50,000 per QALY are [redacted]% and [redacted]%, respectively.

Similarly, based on the list price for givinostat, the probabilistic ICER is £137,832 which is congruent with the deterministic ICER of £141,583. The cost-effectiveness plane and CEAC assuming the list price for givinostat are depicted in Figure 54 and Figure 55, respectively.

**Table 90: Probabilistic results (with PAS)**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs* | Probabilistic ICER (£/QALY)* | Deterministic ICER (£/QALY)* |
|---|---|---|---|---|---|---|
| **Givinostat** | [redacted] | 19.4 | | | | |
| **ECM** | £99,042 | 6.1 | [redacted] | 22.5 | [redacted] | [redacted] |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.
*Including the 1.7 severity modifier


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**Figure 52: Cost-effectiveness plane | 1,000 iterations (with PAS)**



Abbreviations: PAS, patient access scheme; QALY, quality adjusted life year

**Figure 53: Cost-effectiveness acceptability curve | 1,000 iterations (with PAS)**



Abbreviations: NMB, net monetary benefit; PAS, patient access scheme

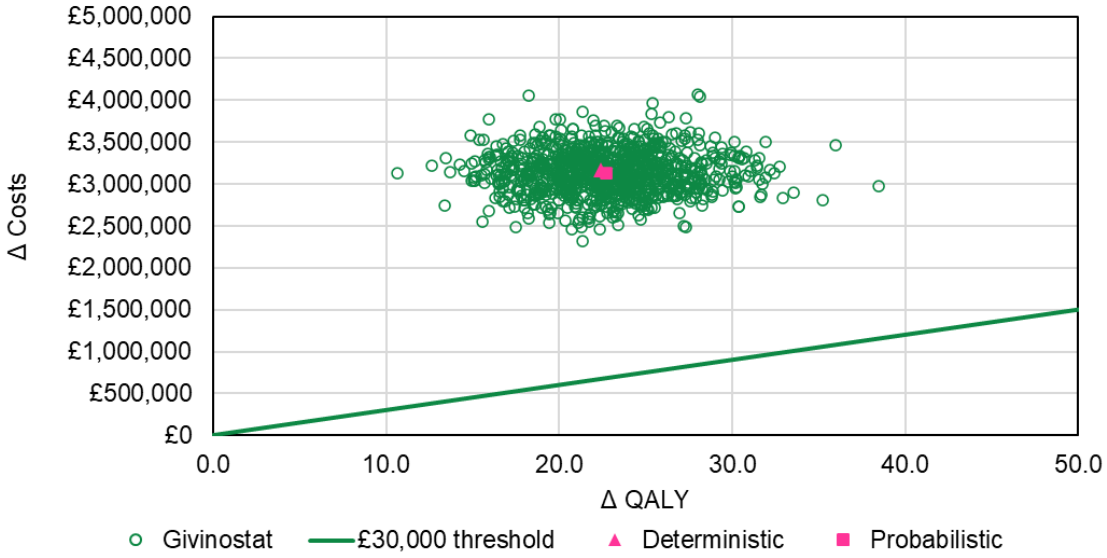
**Table 91: Probabilistic results (list price)**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | Probabilistic ICER (£/QALY) | Deterministic ICER (£/QALY) |
|---|---|---|---|---|---|---|
| **Givinostat** | £3,234,052 | 19.5 | | | | |
| **ECM** | £99,219 | 6.2 | £3,134,833 | 22.7 | £137,832 | £141,583 |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.

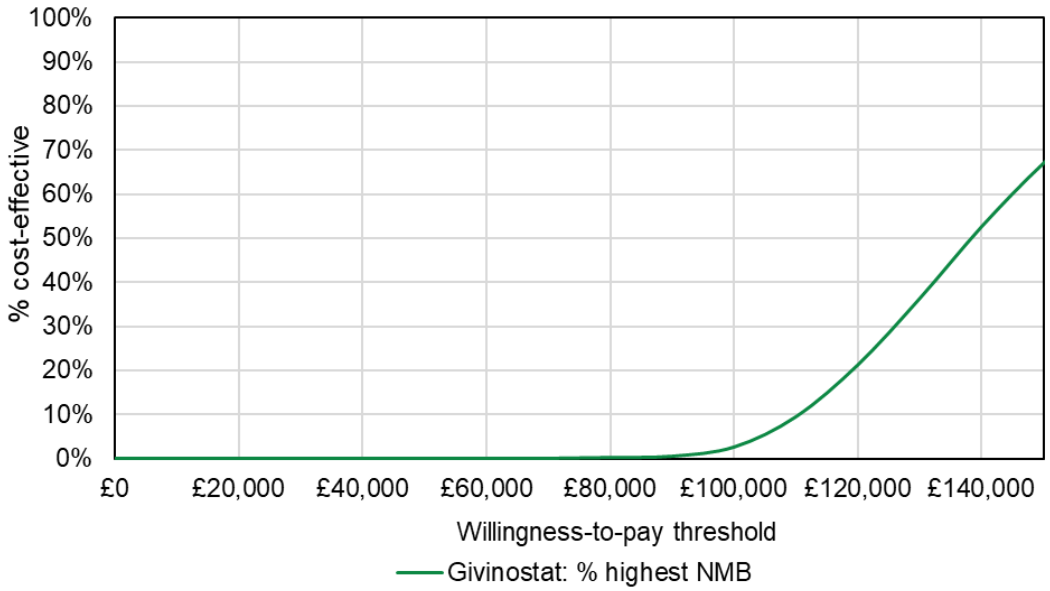

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**Figure 54: Cost-effectiveness plane | 1,000 iterations (list price)**




Abbreviations: QALY, quality adjusted life year.

**Figure 55: Cost-effectiveness acceptability curve | 1,000 iterations (list price)**




Abbreviations: NMB, net monetary benefit.

### B.3.11.2 Deterministic sensitivity analysis

Parameter uncertainty is tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined


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by the 95% CI, estimated based on a standard error calculated as 20% of the mean value for inputs where no estimates of precision were available.

Results for the ten most influential parameters are depicted in a tornado diagram in Figure 56 and detailed in Table 92 using the ICER as the outcome and applying the proposed PAS for givinostat. Figure 57 and Table 92 present the results using the list price for givinostat.

The parameters with the biggest impact on the ICER are the number of caregivers (ICERs with the proposed PAS ranging from [redacted] to [redacted]), the HR applied to transitions from health state (1; early ambulatory) to health state (2; late ambulatory) to estimate givinostat outcomes (ICERs with the proposed PAS ranging from [redacted] to [redacted]), and the number of patients who discontinued givinostat in EPIDYS (ICERs with the proposed PAS ranging from [redacted] to [redacted]).

In the OWSA, the number of caregivers ranges from 1.2 to 2.8 (assuming a standard error of 20% of the mean and a normal distribution). In the base case, two caregivers are assumed. However, as described in Section B.3.4.6, the assumption of two caregivers may be conservative. Therefore, the lower bound in the OWSA is unlikely to be reflective of the number of carers in UK clinical practice. Similarly, the upper bound in the OWSA may still be conservative. A scenario analysis explores the impact of three caregivers on the ICER (Section B.3.11.3); the ICER is shown to reduce from [redacted] to [redacted].

In the OWSA, the uncertainty associated with the HRs is explored by assuming a standard error of 20% of the mean and a log-normal distribution. In relation to the HR applied to transitions from health state (1; early ambulatory) to health state (2; late ambulatory) to estimate givinostat outcomes, it is expected that this transition from the first health state to the next health state would have the biggest impact on the ICER, as this has downstream impacts on all later transitions within the model. The data informing these early transitions are the most robust, with fewer assumptions required in the MAIC analyses compared to the later transitions. Therefore, the uncertainty associated with these early transitions is limited.

The number of patients who discontinued givinostat in EPIDYS directly influences the discontinuation rate from givinostat within the CEM. This then impacts the cost of givinostat within the CEM. Therefore, it is anticipated that this parameter would be a key driver. However, despite a wide confidence interval, based on a standard error of 20% of the mean and a normal distribution, there is a limited impact on results.

Remaining parameters are shown to have a limited impact on results.


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**Figure 56: Tornado diagram | ICER (with PAS)**



Abbreviations: HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

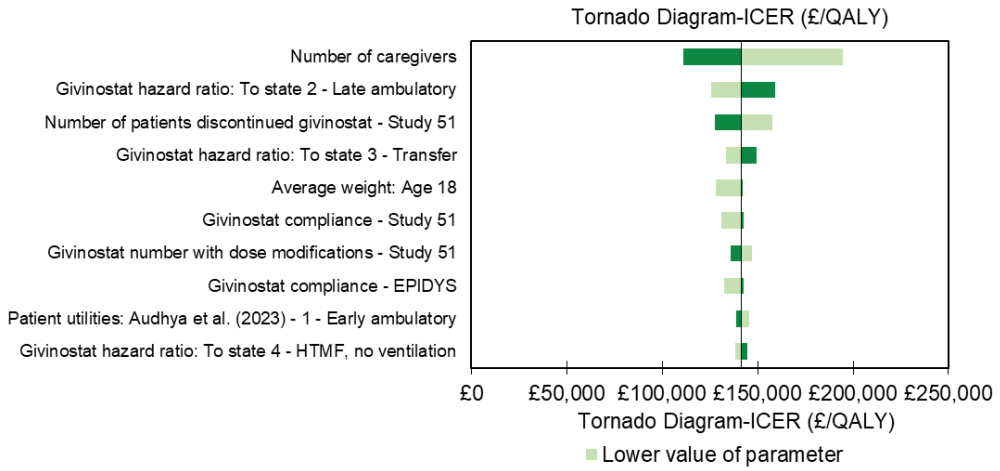
**Table 92: One-way sensitivity analysis (with PAS)**

| Parameter | ICER at upper value of parameter | ICER at lower value of parameter |
|---|---|---|
| Number of caregivers | [redacted] | [redacted] |
| Givinostat HR: To state 2 - Late ambulatory | [redacted] | [redacted] |
| Number of patients discontinuing givinostat - OLE | [redacted] | [redacted] |
| Givinostat HR: To state 3 - Transfer | [redacted] | [redacted] |
| Average weight: Age 18 | [redacted] | [redacted] |
| Givinostat number with dose modifications - OLE | [redacted] | [redacted] |
| Patient utilities: health state 1 - Early ambulatory | [redacted] | [redacted] |
| Givinostat HR: To state 4 - HTMF, no ventilation | [redacted] | [redacted] |
| Givinostat HR: To state 7a - No HTMF, night-time ventilation | [redacted] | [redacted] |
| Caregiver utilities: health state 1 - Early ambulatory | [redacted] | [redacted] |

Abbreviations: HR, hazard ratio; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.


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**Figure 57: Tornado diagram | ICER (with list price)**




Abbreviations: HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

**Table 93: One-way sensitivity analysis (with list price)**

| Parameter | ICER at upper value of parameter | ICER at lower value of parameter |
|---|---|---|
| Number of caregivers | £194,743 | £111,222 |
| Givinostat hazard ratio: To state 2 - Late ambulatory | £125,599 | £159,271 |
| Number of patients discontinued givinostat - Study 51 | £157,604 | £127,484 |
| Givinostat hazard ratio: To state 3 - Transfer | £133,299 | £149,432 |
| Average weight: Age 18 | £128,067 | £141,724 |
| Givinostat compliance - Study 51 | £130,832 | £142,855 |
| Givinostat number with dose modifications - Study 51 | £147,194 | £135,972 |
| Givinostat compliance - EPIDYS | £132,418 | £142,448 |
| Patient utilities: Audhya et al. (2023) - 1 - Early ambulatory | £145,381 | £138,647 |
| Givinostat hazard ratio: To state 4 - HTMF, no ventilation | £138,175 | £144,541 |

Abbreviations: HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

### B.3.11.3 Scenario analysis

Scenario analyses were performed to explore the structural uncertainty within the CEM. A full list of scenarios tested is presented in Table 94. Table 95 and Table 97 present the results from the deterministic scenario analyses, with the proposed PAS and based on the list price for givinostat, respectively.

Based on the scenarios including the PAS, those with the biggest impact on the ICER (defined as ±10.0% compared to the base case) are:


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- The givinostat treatment continuation rule (discontinuation at loss of ambulation vs. no explicit stopping rule, -40.9%, and discontinuation at loss of HTMF vs. no explicit stopping rule, -19.5%),
- The number of caregivers (three vs. two, -25.8%),
- The discount rate applied to outcomes (1.5% across the model time horizon vs. 3.5% for 30 years followed by 1.5%, -18.9%),
- The source of caregiver utilities (Landfeldt et al. 2017 vs. the UK caregiver vignette, -17.4%), and
- The NHM (NHM [updated analysis 1] vs. NHM [updated analysis 2], -16.9%, and NHM [as published] vs. NHM [updated analysis 2], +11.0%).

As described in Section B.3.3.4, in the base case, no explicit treatment continuation rule is assumed for givinostat. The assumption of no explicit treatment continuation rule is supported by feedback from UK clinicians who stated that the decision to continue treatment follows no consistent rule and is based on continuous reviews and discussions with other members of the multi-disciplinary teams, caregivers, and patients. The CEM does reflect a constant discontinuation rate over time based on the data from EPIDYS and the OLE study. However, there is no explicit treatment continuation rule whereby all patients continue until a defined point. Due to the variation in clinical practice, different treatment continuation rules may be relevant in some cases. The treatment continuation rules are shown to reduce the ICER, indicating that the base case may be conservative.

As described in Section B.3.4.6, in the base case, two caregivers are assumed per patient with DMD. However, the assumption of two caregivers may be conservative. Therefore, a scenario explores three caregivers and demonstrates that if additional caregivers are relevant, the ICER reduces.

As described in Section B.3.2.2, in the base case, outcomes are discounted at 3.5% per annum for the first 30 years, after this point, outcomes are discounted at 1.5% per annum. However, the scenario exploring 1.5% for outcomes across the model time horizon may be more relevant; givinostat meets two of the three criteria specified in the NICE Manual for non-reference discounting i.e., givinostat is for people who have a very severely impaired life and the benefits of givinostat are likely to be sustained over a very long period. Although, givinostat does not restore patients to full or near-full health (the final criteria), givinostat extends the time in which patients maintain in earlier health states which are associated with improved HRQoL. Additionally, the scenario exploring 1.5% for outcomes across the model time horizon is supported by the HM Treasury Green Book; this source states that 1.5% is the relevant discount rate when assessing QALYs. The HM Treasury Green Book takes this further and states that QALYs should be discounted based on 1.5% for 30 years, and after this point should have a reduced discount rate over time. Therefore, the base case uses a conservative estimate; aligning with the non-reference case as per the NICE Manual or the HM Treasury Book reduces the ICER.

As described in Section B.3.4.3, in the base case, the UK caregiver vignette study was selected to inform caregiver utilities. The scenario analysis explores the impact of applying the caregiver utilities reported in Landfeldt et al. 2017 as per previous NICE appraisals in


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DMD; the results indicate that the base case is conservative, as using Landfeldt et al. 2017 results in a reduction in the ICER.

As described in Section B.3.3.1, the original published NHM does not align with expected UK clinical practice – as acknowledged in the ongoing vamorolone NICE appraisal. However, this is shown for consistency with the ongoing appraisal. Whilst the outcomes predicted by the updated NHM (analysis 1) are similar to the updated NHM (analysis 2 - Table 47); the predicted median age at loss of ambulation, starting nighttime ventilation, and starting fulltime ventilation from the updated NHM (analysis 2) are more closely aligned with the UK real-world data. Therefore, the updated NHM (analysis 2) is the most externally valid option to inform the base case.

Due to the number of scenario analyses explored, the scenarios that demonstrated the biggest impact on the cost-effectiveness results in the deterministic analyses were conducted probabilistically. Therefore, the scenarios exploring givinostat treatment continuation rules, the number of caregivers, the discount rate applied to outcomes, the source of caregiver utilities, and the NHM are explored probabilistically. Probabilistic scenario analyses involved running the PSA across 1,000 iterations, under the assumptions of each scenario, methods aligning with the base case PSA in Section B.3.11.1. Table 96 and Table 98 present the results of the probabilistic scenario analyses compared to the base case probabilistic ICERs including the PAS and based on the list price for givinostat, respectively. Probabilistic scenario results are shown to be highly congruent to deterministic scenario analyses.


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**Table 94: Scenario analyses**

| | Base case | Scenario | Rationale |
|---|---|---|---|
| **Time horizon** | Lifetime (70 years) | 50 years | DMD is a lifelong illness, and treatment with givinostat can be given across a patient's lifetime. Therefore, a lifetime horizon is applied. Scenario analyses explore the uncertainty associated with the definition of lifetime |
| | | 60 years | |
| **Perspective** | NHS and PSS perspective | Societal perspective using Landfeldt et al. 2014; 2017[56, 192] | Aligning with the NICE reference case. However, scenario analyses explore the additional impact relevant to this disease setting from societal costs |
| | | Societal perspective using the Project HERCULES UK BOI study[193] | |
| **Discount rate** | 3.5% costs<br>3.5% outcomes for 30 years, followed by 1.5% | 3.5% costs<br>1.5% outcomes across model time horizon | Aligning with the NICE reference case and guidance presented in the HM Treasury Green Book. A scenario analysis explores the non-reference case from the NICE Manual which may be appropriate for givinostat |
| **Comparator** | Distribution and dosing schedule of CS and from EPIDYS | Distribution and dosing schedule of CS from UK real-world data | Aligning with the clinical data underpinning the relative efficacy in the CEM. A scenario analysis explores the real-world distribution of CS and intermittent vs. daily dosing based on UK clinical practice |
| **NHM** | Updated NHM (analysis 2) | Updated NHM (analysis 1) | The base case uses external data (published literature, UK real-world data, and UK clinical opinion) to ensure the NHM is externally valid. Scenario analyses explore the uncertainty associated with the NHM |
| | | Published NHM | |
| **Source for treatment duration, adverse events, compliance, and dose modifications** | Weighted data from EPIDYS and the OLE study for treatment duration, adverse events, compliance, and dose modifications | Data from EPIDYS for treatment duration, adverse events, compliance, and dose modifications | The EPIDYS and OLE data provide the longest follow-up for givinostat. Therefore, these data inform the CEM in the base case. A scenario analysis explores the use of the data from EPIDYS only |


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| | | | |
|---|---|---|---|
| **Givinostat treatment continuation rules** | No explicit treatment continuation rule | Treatment continuation until fulltime ventilation | Based on UK clinical feedback, no explicit treatment continuation rule is assumed for givinostat in the base case. Scenario analyses explore the impact of treatment continuation rules for givinostat |
| | | Treatment continuation until loss of HTMF | |
| | | Treatment continuation until loss of ambulation | |
| **CS treatment continuation rules** | No explicit treatment continuation rule | Treatment continuation until fulltime ventilation | Based on UK clinical feedback, no explicit treatment continuation rule is assumed for CS in the base case. Scenario analyses explore the impact of treatment continuation rules for CS |
| | | Treatment continuation until loss of HTMF | |
| | | Treatment continuation until loss of ambulation | |
| **Patient utilities** | Audhya et al. 2023[95] | Landfeldt et al. 2017[192] | The measurements in Audhya et al. 2023 align with the health states specified in the CEM and the methods for determining utilities align with the NICE reference case i.e. the EQ-5D measure was used and self-reported by patients. This study is also the most recent patient HRQoL data available in DMD. Scenario analyses explore alternative sources for patient utilities. |
| | | Project HERCULES UK BOI study[239] | |
| **Number of caregivers** | Two | Three | Although the assumption of two caregivers may be conservative, in the absence of data from which to estimate the precise number of caregivers, two are assumed in the base case. A scenario analyses explores the impact of three caregivers. |
| **Caregiver utilities** | UK vignette study[98] | Landfeldt et al. 2017 | In the base case, values are sourced from the UK caregiver vignette study which aligns with the granularity of the Project HERCULES NHM. A scenario analysis explores an alternative source for caregiver utilities. |
| **Caregiver utilities approach** | Caregiver increments relative to the midway health state | Caregiver utilities | The caregiver increments relative to the midway health state reflects the impact of |


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| | | | |
|---|---|---|---|
| | | Caregiver disutilities | givinostat in UK clinical practice; increased LYs spent caring for a patient in the ambulatory health states accrue a positive increment and increased LYs spent caring for a patient in the late-stage health states or death accrue a negative decrement. These directions align with expectations as to the impact of a new intervention for DMD. Alternative approaches are explored in scenario analyses and demonstrate no impact on the ICER. |
| | | Caregiver increments relative to the worst health state | |
| **Health state costs** | Project HERCULES UK CPRD study[238] | Landfeldt et al. 2014; 2017 | The Project HERCULES UK CPRD study data reflect a large cohort, are UK-specific, represent the most recent data and align with the NICE reference case. Additionally, the costs are shown to increase as the disease progresses across the health states. Scenario analyses explore alternative sources for health state costs. |
| | | Project HERCUES UK BOI study | |

Abbreviations: BOI, burden of illness; CEM, cost-effectiveness model; CPRD, Clinical Practice Research Datalink; CS, corticosteroids; DMD, Duchenne muscular dystrophy; EAG, Evidence Assessment Group; ECM, established clinical management; EQ-5D, EuroQol 5-dimensions; HRQoL, health-related quality of life; HTMF, hand-to-mouth function; NICE, National Institute for Health and Care Excellence; NHM, natural history model; OLE, open-label extension; QALY, quality adjusted life year.


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**Table 95: Deterministic scenario analyses (with PAS)**

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | % change from base-case ICER |
|---|---|---|---|---|
| Base-case | [redacted] | 22.4 | [redacted] | 0.0% |
| Time horizon: 50 years | [redacted] | 20.9 | [redacted] | 6.7% |
| Time horizon: 60 years | [redacted] | 22.0 | [redacted] | 1.8% |
| Perspective: Societal using Landfeldt et al. | [redacted] | 22.4 | [redacted] | 7.6% |
| Perspective: Societal using Project HERCULES BOI | [redacted] | 22.4 | [redacted] | 7.4% |
| Discount rates: 3.5% costs and 1.5% outcomes across model time horizon | [redacted] | 27.6 | [redacted] | -18.9% |
| Distribution and dosing schedule for CS: UK real-world data | [redacted] | 22.4 | [redacted] | 0.5% |
| NHM: Updated analysis 1 | [redacted] | 28.2 | [redacted] | -16.9% |
| NHM: Original | [redacted] | 21.6 | [redacted] | 11.0% |
| Source for treatment duration, adverse events, compliance, and dose modifications: EPIDYS | [redacted] | 22.4 | [redacted] | -9.4% |
| Givinostat continuation rule: until fulltime ventilation | [redacted] | 22.4 | [redacted] | -4.6% |
| Givinostat continuation rule: until loss of HTMF | [redacted] | 22.4 | [redacted] | -19.5% |
| Givinostat continuation rule: until loss of ambulation | [redacted] | 22.4 | [redacted] | -40.9% |
| CS continuation rule: until fulltime ventilation | [redacted] | 22.4 | [redacted] | 0.0% |
| CS continuation rule: until loss of HTMF | [redacted] | 22.4 | [redacted] | -0.2% |
| CS continuation rule: until loss of ambulation | [redacted] | 22.4 | [redacted] | -0.4% |
| Patient utilities: Landfeldt et al. | [redacted] | 21.7 | [redacted] | 3.4% |
| Patient utilities: Project HERCULES BOI | [redacted] | 23.0 | [redacted] | -2.4% |
| Number of caregivers: three | [redacted] | 30.2 | [redacted] | -25.8% |
| Caregiver utilities: Landfeldt et al. | [redacted] | 27.1 | [redacted] | -17.4% |
| Caregiver HRQoL approach: utilities | [redacted] | 22.4 | [redacted] | 0.0% |
| Caregiver HRQoL approach: disutilities | [redacted] | 22.4 | [redacted] | 0.0% |
| Caregiver HRQoL approach: increments relative to severe | [redacted] | 22.4 | [redacted] | 0.0% |


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| | | | | |
|---|---|---|---|---|
| Health state costs: Landfeldt et al. | [redacted] | 22.4 | [redacted] | 2.8% |
| Health state costs: Project HERCULES BOI | [redacted] | 22.4 | [redacted] | -0.2% |

Abbreviations: BOI, burden of illness; CS, corticosteroids; ECM, established clinical management; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; NHM, natural history model; OLE, open-label extension; PAS, patient access scheme.


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**Table 96: Probabilistic scenario analyses (with PAS)**

| Scenario | Deterministic ICER (£/QALY) | Probabilistic ICER (£/QALY) |
|---|---|---|
| Base case | [redacted] | [redacted] |
| Discount rates: 3.5% costs and 1.5% outcomes across model time horizon | [redacted] | [redacted] |
| NHM: Updated analysis 1 | [redacted] | [redacted] |
| NHM: Original | [redacted] | [redacted] |
| Givinostat continuation rule: until loss of HTMF | [redacted] | [redacted] |
| Givinostat continuation rule: until loss of ambulation | [redacted] | [redacted] |
| Number of caregivers: three | [redacted] | [redacted] |
| Caregiver utilities: Landfeldt et al. | [redacted] | [redacted] |

Abbreviations: BOI, burden of illness; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme.


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**Table 97: Deterministic scenario analyses (list price)**

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | % change from base-case ICER |
|---|---|---|---|---|
| Base-case | £3,172,896 | 22.4 | £141,583 | 0.0% |
| Time horizon: 50 years | £3,159,149 | 20.9 | £151,210 | 6.8% |
| Time horizon: 60 years | £3,170,208 | 22.0 | £144,227 | 1.9% |
| Perspective: Societal using Landfeldt et al. | £3,273,373 | 22.4 | £146,066 | 3.2% |
| Perspective: Societal using Project HERCULES BOI | £3,270,060 | 22.4 | £145,918 | 3.1% |
| Discount rates: 3.5% costs and 1.5% outcomes across model time horizon | £3,172,896 | 27.6 | £114,828 | -18.9% |
| Distribution and dosing schedule for CS: UK real-world data | £3,179,955 | 22.4 | £141,898 | 0.2% |
| NHM: Updated analysis 1 | £3,313,012 | 28.2 | £117,565 | -17.0% |
| NHM: Original | £3,430,817 | 21.6 | £158,937 | 12.3% |
| Source for treatment duration, adverse events, compliance, and dose modifications: EPIDYS | £2,871,257 | 22.4 | £128,191 | -9.5% |
| Givinostat continuation rule: until full time ventilation | £3,023,890 | 22.4 | £134,930 | -4.7% |
| Givinostat continuation rule: until loss of HTMF | £2,547,144 | 22.4 | £113,648 | -19.7% |
| Givinostat continuation rule: until loss of ambulation | £1,860,159 | 22.4 | £82,986 | -41.4% |
| CS continuation rule: until full time ventilation | £3,172,690 | 22.4 | £141,576 | 0.0% |
| CS continuation rule: until loss of HTMF | £3,170,599 | 22.4 | £141,481 | -0.1% |
| CS continuation rule: until loss of ambulation | £3,167,660 | 22.4 | £141,348 | -0.2% |
| Patient utilities: Landfeldt et al. | £3,172,896 | 21.7 | £146,388 | 3.4% |
| Patient utilities: Project HERCULES BOI | £3,172,896 | 23.0 | £138,125 | -2.4% |
| Number of caregivers: three | £3,172,896 | 30.2 | £105,017 | -25.8% |
| Caregiver utilities: Landfeldt et al. | £3,172,896 | 27.1 | £116,919 | -17.4% |
| Caregiver HRQoL approach: utilities | £3,172,896 | 22.4 | £141,583 | 0.0% |
| Caregiver HRQoL approach: disutilities | £3,172,896 | 22.4 | £141,583 | 0.0% |
| Caregiver HRQoL approach: increments relative to the worst health state | £3,172,896 | 22.4 | £141,583 | 0.0% |


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| | | | | |
|---|---|---|---|---|
| Health state costs: Landfeldt et al. | £3,210,141 | 22.4 | £143,245 | 1.2% |
| Health state costs: Project HERCULES BOI | £3,170,141 | 22.4 | £141,460 | -0.1% |

Abbreviations: BOI, burden of illness; CS, corticosteroids; ECM, established clinical management; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; NHM, natural history model; OLE, open-label extension.


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**Table 98: Probabilistic scenario analyses (list price)**

| Scenario | Deterministic ICER (£/QALY) | Probabilistic ICER (£/QALY) |
|---|---|---|
| Base-case | £141,583 | £138,756 |
| Discount rates: 3.5% costs and 1.5% outcomes across model time horizon | £114,828 | £113,105 |
| NHM: Updated analysis 1 | £117,565 | £115,473 |
| NHM: Original | £158,937 | £155,112 |
| Givinostat continuation rule: until loss of HTMF | £113,648 | £110,806 |
| Givinostat continuation rule: until loss of ambulation | £82,986 | £81,217 |
| Number of caregivers: three | £105,017 | £101,804 |
| Caregiver utilities: Landfeldt et al. | £116,919 | £113,660 |

Abbreviations: ECM, established clinical management; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; NHM, natural history model; QALY, quality adjusted life year.


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## *B.3.12 Validation*

### B.3.12.1 Internal validation of cost-effectiveness analysis

A quality check of the electronic CEM was conducted by an external health economist who was not involved in the development of the model. The quality check was based on a targeted sheet-by-sheet approach and checklists published in Drummond et al. 1996, Phillips et al. 2004, and the NICE manual.[242, 243] The review assessed the accuracy and transparency of the model calculations and functionality. The review also advised on the validity of the modelling approach, and whether any specific base-case model settings and assumptions required further justification. Topics identified as part of the quality check have been addressed in the version of the CEM included alongside this submission.

In addition to the internal validation checks described above, the CEM developed by Project HERCULES underwent multiple rounds of internal and external validation prior to being finalized.

### B.3.12.2 External validation of cost-effectiveness analysis

The published NHM underwent extensive validation as part of the updates described in Section B.3.3.1. To ensure that the NHM informing the CEM is externally valid and relevant to UK clinical practice, adjustments were made to align the NHM with UK real-world data and UK clinical feedback from the medical advisory board conducted in April 2024.[19, 20, 178] These data sources are detailed in Section B.3.3.1 and are compared with the published and updated NHMs. Predicted outcomes are shown to closely align with these data sources.

Additional data have been obtained from the NorthStar UK registry for the number of patients who are ambulant and non-ambulant across ages 6–18 years; these data are presented in Table 99 and compared to the model predictions for ECM.[32] The base case model predictions, based on the updated NHM (analysis 2) are shown to closely align with the NorthStar data; it is expected that the model predictions are slightly higher than the NorthStar data based on the requirement for ambulant status at baseline (age 6). These data further support the use of the updated NHM (analysis 2) in the base case.


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**Table 99: A comparison of NorthStar ambulation status data with the ECM model predictions***

| Age | NorthStar data | | ECM – Model predictions | |
|---|---|---|---|---|
| | Ambulant | Non-ambulant | Ambulant | Non-ambulant |
| 6 | 21 (95.5%) | 1 (4.5%) | 100.0% | 0.0% |
| 7 | 25 (92.6%) | 2 (7.4%) | 98.9% | 1.1% |
| 8 | 41 (95.3%) | 2 (4.7%) | 93.4% | 6.6% |
| 9 | 29 (76.3%) | 9 (23.7%) | 84.3% | 15.7% |
| 10 | 43 (79.6%) | 11 (20.4%) | 73.5% | 26.5% |
| 11 | 42 (72.4%) | 16 (27.6%) | 62.5% | 37.5% |
| 12 | 30 (45.5%) | 36 (54.5%) | 52.3% | 47.7% |
| 13 | 34 (47.9%) | 37 (52.1%) | 43.3% | 56.7% |
| 14 | 17 (30.4%) | 39 (69.6%) | 35.6% | 64.4% |
| 15 | 19 (28.4%) | 48 (71.6%) | 29.2% | 70.8% |
| 16 | 16 (22.9%) | 54 (77.1%) | 23.9% | 76.1% |
| 17 | 17 (25.4%) | 50 (74.6%) | 19.6% | 80.4% |
| 18+ | 30 (13.8%) | 188 (86.2%) | 16.1% | 83.9% |

*Note: these data reflect a snapshot in time and are not cumulative.
Abbreviations: ECM, established clinical management.

Additional data have also been obtained through a descriptive study using the Hospital Episodes Statistics (HES) dataset to explore the healthcare utilisation, costs, and life expectancy associated with ECM for DMD in England.[36, 244]

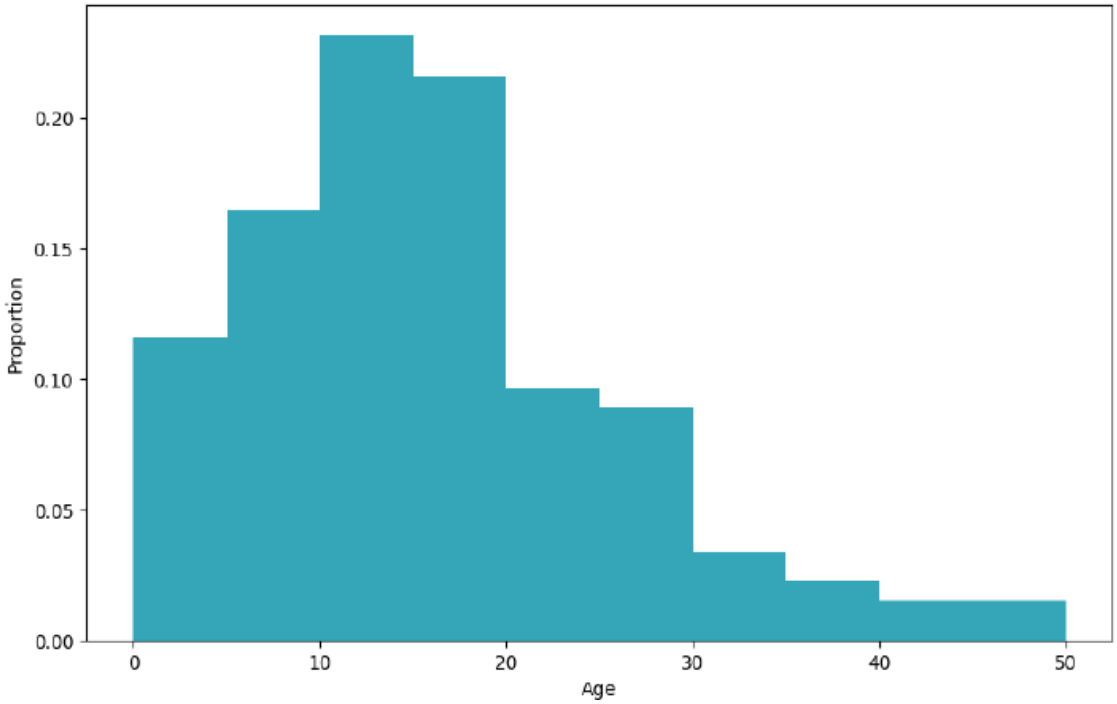
A total of 7,718 patients were identified in the HES data set with ICD-10 code for muscular dystrophy (G71.0) recorded in any of the 20 diagnosis fields from April 2019 to March 2024. Six explicit exclusion criteria were applied to distinguish patients with DMD from the cohort: (1) female patients were excluded as DMD predominantly occurs in males (N=2,752 excluded), (2) patients diagnosed after eight years of age were excluded as DMD is predominantly diagnosed in early childhood (N=24 excluded), (3) patients aged over 50 years of age were excluded as, based on clinical feedback, it is unlikely that many patients with DMD will survive beyond age 50 (N=1,730 excluded), (4) patients with ICD-10 codes for other forms of muscular disorders were excluded (N=547 excluded), (5) patients aged over 20 years of age without recorded ambulation issues were excluded aligned with previous studies and clinical feedback (N=630 excluded), and (6) patients aged over 30 years of age without recorded ventilation issues were excluded aligned with clinical feedback (N=95). This resulted in 1,937 patients comprising the cohort described in this submission and assumed to represent patients with DMD in England.

Figure 58 presents the distribution of patients by age group; the mean age across all patients was 16.7 (SD: 9.7). The mean age predicted by the ECM arm in the CEM is 18.8 – this closely aligns with the data from the HES study. The HES study identified N=976 patients with abnormal ambulation and N=650 patients who had been ventilated in the previous 5-years. The mean age of patients in the HES data set with abnormal ambulation was 22.7 (SD: 9.5) and with ventilation was 25.4 (SD: 9.6). The mean ages predicted by the


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ECM arm in the CEM for these patients are 22.9 and 25.1, respectively – closely aligning with the data from the HES study.

**Figure 58: Study cohort assumed to have DMD in the HES dataset by age group[36]**




Abbreviations: DMD, Duchenne muscular dystrophy; HES, Hospital Episode Statistics.

The HES study explores age of death through two methods: (1) analysing known inpatient deaths for patients assumed to have DMD within the past 5-years and (2) analysing presumed deaths of patients assumed to have DMD who have not had recorded activity in the HES data set for the past two years. In method (1), the study identified 116 patients who died in the past five years (April 2019 – March 2024). The average age of death was 28 years across these 116 patients. In method (2), the study identified 40 patients who had no health records in the past two years and who were assumed to have died (April 2022 – March 2024). The average age of death was 23 years across these 40 patients. The average age of death in the CEM is 27.1 – closely aligning with the data from the HES study.

The HES dataset is unable to identify deaths of patients who passed away in the community – this is a key limitation as reportedly a large proportion of patients with DMD die in community settings. Additionally, the presumed death analysis infers that the death of a patient has occurred if they have had a history of recorded care but have not had inpatient, outpatient, or emergency activity in the past two years. Therefore, it is unable to distinguish non-activity in the past two years because of other reasons e.g. the patient has moved to another country. Despite these limitations, the average age of death observed in the HES analyses (23-28 years) aligns with the mean age of death predicted by the CEM for patients treated with ECM (27.1).


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Table 54 presents the median age patients reach key disease milestones predicted by the CEM; for the ECM arm these are aligned with UK real-world data (Section B.3.3.3), as well as the UK NorthStar and HES data described above. The values predicted in the givinostat arm align with the median ages at key milestones derived from parametric curves fit to the MAIC-weighted Kaplan-Meier data.

One study considering a UK perspective was identified in the economic SLR (Section B.3.1) reporting total QALYs and total costs for the ECM arm (Landfeldt et al. 2017).[192] Total patient QALYs reported in Landfeldt et al. 2017 ranged from 6.0 to 7.2 across the three model structures – this aligns with this submission where 6.1 patient QALYs are predicted in the ECM arm. Total caregiver QALYs when including one caregiver reported in Landfeldt et al. 2017 ranged from 12.7 to 12.8 – this aligns with the predictions from the CEM when one caregiver and caregiver utilities is assumed (12.0 caregiver QALYs in the ECM arm). Note: this submission assumes two caregivers and applies increments relative to the midway health state in the base case. The ongoing vamorolone NICE submission also reports the EAG corrected base case total QALYs for ECM. Total QALYs from the EAG corrected base case range from 10.6 to 10.7 for ECM. However, this appraisal is ongoing and base case assumptions informing the first Committee meeting were re-visited in the second Committee meeting. It is also unclear how these have been derived in terms of the NICE severity modifier and the number of caregivers assumed. Furthermore, following the first Committee meeting, the Committee concluded that outcomes may be over-estimated in the ECM arm.

## *B.3.13 Interpretation and conclusions of economic evidence*

### B.3.13.1 Main findings

The analysis indicates that givinostat is associated with an incremental LY and QALY gain of 7.3 and 22.4 (13.2 without the severity modifier) compared with ECM, respectively, at an additional cost of £[redacted]. The resulting ICER for givinostat vs. ECM is £[redacted] per QALY gained – based on the proposed PAS for givinostat and the 1.7 severity modifier.

The increased LYs and QALYs predicted by the analysis are driven by the improved outcomes observed with givinostat in EPIDYS and the OLE study for age at loss of ambulation compared to UK real-world data for ECM; a MAIC analysis of these data estimated a HR of 0.185 (95% CI: 0.121 – 0.282) for givinostat relative to ECM. The MAICs also estimate HRs of 0.190 (95% CI: 0.124 – 0.290) and 0.214 (95% CI: 0.139 – 0.329) for age at non-invasive ventilation and age at FVC<1L for givinostat vs. ECM, based on the improvement observed for age at loss of ambulation and the relationship between this early outcome and the longer-term outcomes observed in patients receiving ECM in the UK real-world data and the literature. These benefits are supported by meaningful improvements observed in other endpoints not used in the modelling: compared with ECM, givinostat slows decline in the ability to climb four stairs, maintains the ability to run, jump, hop and rise from the floor/a chair for longer, slows decline in muscle strength in both lower and upper limbs, and slows fat infiltration in muscles (Section B.2.12).

Whilst givinostat is associated with greater total costs vs. ECM, givinostat is associated with cost savings in full-time ventilation costs ([redacted]) and spinal fusion surgery costs ([redacted]). These savings are driven by givinostat prolonging the time to reach full-time ventilation compared to ECM and a lower rate of scoliosis requiring spinal fusion surgery.


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Results are shown to be robust in a series of sensitivity analyses, including PSA, OWSA, and scenario analyses. The results are most sensitive to the approach to assumptions associated with the givinostat treatment continuation rule (discontinuation at loss of ambulation vs. no explicit stopping rule, [redacted]%, and discontinuation at loss of HTMF vs. no explicit stopping rule, [redacted]%), the number of caregivers (three vs. two, [redacted] %), the discount rate assumed for outcomes (1.5% across the model time horizon vs. 3.5% for 30 years followed by 1.5%, [redacted] %), the source of caregiver utilities (Landfeldt et al. 2017 vs. the UK caregiver vignette, [redacted]%), and the NHM (NHM [updated analysis 1] vs. NHM [updated analysis 2], [redacted] %, and NHM [as published] vs. NHM [updated analysis 2], [redacted] %). Except for variations of the NHM, these scenarios are shown to reduce the ICER, indicating that the base case ICER may be conservative.

As detailed in Section B.3.2, givinostat meets two of the three criteria specified in the NICE Manual for non-reference discounting i.e., givinostat is for people who have a very severely impaired life and the benefits of givinostat are likely to be sustained over a very long period. Although, givinostat does not restore patients to full or near-full health (the final criteria), givinostat extends the time in which patients maintain in earlier health states which are associated with improved HRQoL. The base case assumes a 3.5% discount rate for outcomes for 30 years, followed by 1.5% based on recommendations outlined in the HM Treasury Green Book. The non-reference 1.5% discount rate ensures that the longer-term benefits of givinostat are appropriately valued within the CEM. Aligning with the requirements specified in the NICE manual for consideration of a non-reference case discount rate, it is expected that the early benefits observed with givinostat will accumulate over time with downstream benefits on HTMF function, lung function, and mortality. Therefore, not only will the treatment benefit be maintained, but it will continue to translate to other improvements over time. The impact of a 1.5% discount for outcomes across the model time horizon is presented in the scenario analyses (Section B.3.11.3); this scenario highlights the potential for under-valuing the benefits which would be achieved through treatment with givinostat.

There may be benefits related to givinostat which are not reflected in the base case ICER. The CEM includes caregiver utilities for two caregivers. Assuming that a DMD diagnosis only effects two caregivers in a family is likely to substantially underestimate the potential burden of this debilitating disease. About one-third of parents believe that DMD has a negative influence on the psychological well-being and social life of the unaffected siblings.[94] Grandparents and other informal caregivers are also negatively impacted due to the increased burden on the family, and an increased need for informal care for boys with DMD.

### B.3.13.2 Strengths and limitations

A key strength of the CEM is that it is informed by the output from Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis), a unique initiative, led by Duchenne UK, to develop tools and evidence to support HTA and reimbursement decisions for new treatments for DMD. Use of the Project HERCULES CEM ensures that the model structure represents the disease and treatment pathway, as validated by published literature, and input from clinicians, academics, patients, and caregivers. The NHM developed as part of Project HERCULES meta-analysed all data that were available in DMD at the time. UK real-world data and feedback from two UK advisory boards have been used to update the NHM to ensure outcomes align with those expected in clinical practice –


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outcomes have been further validated by comparisons with data from the NorthStar registry and HES data set (Section B.3.12).

A further strength of the CEM is that the relative efficacy of givinostat is informed by data form EPIDYS and the OLE study. The Phase 3 EPIDYS study provides comparative evidence on the efficacy of givinostat vs. ECM in one of the largest Phase 3 RCTs in DMD across an unprecedented follow-up period. The results of EPIDYS demonstrate that givinostat positively impacts the trajectory of the disease and preserves muscle mass and function compared with ECM. The ongoing the OLE study provides long-term safety and efficacy data for givinostat. Initial results from the OLE study (Dec 2021 DCO) show efficacy and safety results that are consistent with those seen in EPIDYS.

Other inputs informing the CEM relating to costs and utilities are informed by SLRs which have been conducted in line with SLR best practices and NICE requirements.[200] Feedback from previous appraisals to NICE in DMD (the ongoing vamorolone NICE appraisal [GID-TA11135] and the ataluren NICE appraisal [HST22]) have been integrated and addressed throughout this submission.[7, 130] Where possible, the NICE reference case as stipulated in the NICE manual has been adhered to and referenced.

The typical limitations and challenges of modelling the cost-effectiveness of treatments for children with long-term outcomes beyond the clinical trial data are relevant here. Whilst the benefit of givinostat has been demonstrated in early outcomes, the CEM also considers longer-term outcomes for which events have not yet been observed in the data. Therefore, the CEM relies on information observed with ECM in the literature and UK real-world data to predict the relationship between the earlier outcomes and the longer-term outcomes. As the same relationship is assumed for givinostat as ECM, these assumptions are considered conservative; givinostat may have an exaggerated impact on these later outcomes.

Although obvious humanistic and clinical value, improving prognosis for survival in DMD is associated with challenges when attempting to demonstrate cost-effectiveness.[245] Despite the obvious benefit and value to patients with DMD from improving prognosis and survival, DMD is associated with chronic care needs and is thus a costly disease to society. Due to the multi-dimensional impact of the disease on patients' health, HRQoL in DMD is typically found to be relatively poor. Therefore, in cost-effectiveness analyses, these two aspects mean that treatments that prolong survival will be associated with only modest benefit (low incremental QALYs), but at the same time a substantial cost (high incremental costs). While ethical and health economic aspects of this phenomenon have been discussed in the literature, the focus has been on end-of-life treatments indicated for patients with a short life expectancy, for example end-stage cancer drugs. However, challenges of including efficacy on mortality in cost-effectiveness analyses are also relevant to treatments targeting chronic diseases associated with extensive care needs and poor HRQoL, such as DMD. Additional research is needed to further examine the public's views on the relative value of life-extending treatments, as well as therapies targeting rare as opposed to common illnesses, to help align health policy with the preferences of the general population.

### B.3.13.3 Conclusions

In line with the improved ability to climb four stairs, ability to run, jump, hop and rise from the floor/a chair, muscle strength in both lower and upper limbs, fat infiltration in muscles, and


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ambulation outcomes observed with givinostat compared to ECM in EPIDYS and the ongoing long-term follow-up demonstrating efficacy and safety of givinostat in the OLE study, this analysis demonstrates that givinostat is associated with an incremental LY and QALY gain of 7.3 and 22.4 (13.2 without the severity modifier) compared to ECM, respectively, at an additional cost of £[redacted]. The resulting ICER for givinostat vs. ECM is £[redacted] per QALY gained – including the proposed PAS for givinostat and the 1.7 severity modifier.

Overall, a positive NICE recommendation for givinostat would provide boys and young men with DMD, their caregivers and clinicians with a new oral treatment option that significantly slows the trajectory of the DMD muscle impairment, reduces decline in muscle mass and potentially delays loss of ambulation and other major disease milestones, compared with ECM.


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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over

# [ID6323]

## Summary of Information for Patients (SIP)

**December 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6323_Givinostat_DMD_SIP_[noCON] | 1.0 | No | 3 December 2024 |

# Summary of Information for Patients (SIP):

### The pharmaceutical company perspective

## What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

## SECTION 1: Submission summary

**1a) Name of the medicine** (generic and brand name):

| |
|---|
| Generic: Givinostat<br>Brand name: Duvyzat® |

**1b) Population this treatment will be used by.** Please outline the main patient population that is being appraised by NICE:

| |
|---|
| Boys and young men with Duchenne muscular dystrophy (DMD) 6 years of age and older, who can walk (ambulant) when they start givinostat; this includes patients that lose the ability to walk (become non-ambulant) during treatment with givinostat. |

**1c) Authorisation:** Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

| |
|---|
| Givinostat was approved for the treatment of DMD in patients 6 years of age and older by the US Food and Drug Administration (FDA) on 21st March 2024.<br>A marketing authorisation application has been submitted to the UK Medicines and Healthcare Regulatory Agency (MHRA) for the treatment of DMD in patients 6 years of age and older, with anticipated approval in early 2025. |

**1d) Disclosures.** Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

| |
|---|
| Duchenne UK and Action Duchenne reviewed sections of the NICE dossier.<br>1. Sponsorship (Friends level, lowest, £10,000) of the Duchenne UK, 2024 New Horizons Conference (1st–2nd March 2024) to support, in a strictly hands-off manner, the organisation and delivery of the conference. Tangible benefits of the sponsorship included 2 x complimentary places for the conference, verbal acknowledgement of sponsorship |

during opening/closing remarks, inclusion of company logo on conference webpage and big screen, printed brochure/agenda, erection of a company branded pull-up banner within the conference auditorium.

2. Sponsorship (Bronze level; lowest, £3,500) of the 17th Muscular Dystrophy UK, UK Neuromuscular Translational Research Conference, 17th–18th April 2024, to support, in a strictly hands-off manner, the organisation and delivery of the conference. Tangible benefits of the sponsorship included company logo within abstract supplement; company logo and short description within event brochure, company logo on intro slides and screensaver during the conference.

3. Sponsorship (Gold level, lowest, £15,000) of the Action Duchenne International Conference 2024 (8th–9th November 2024) to support, in a strictly hands-off manner, the organisation and delivery of the conference. Tangible benefits of the sponsorship to include 3 complimentary passes, 4 acknowledgements as a sponsor on promotional e-mails, recognition of company sponsorship on the conference event website, and recognition of sponsorship on the conference programme/agenda.

# SECTION 2: Current landscape

### 2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained

**Duchenne muscular dystrophy (DMD)**

DMD is a rare, progressive, lethal neuromuscular disorder that almost exclusively affects boys due to mutations in the dystrophin gene located on an X chromosome.[1,2] As boys only have one X chromosome, a mutation in this gene means the body can't make functional dystrophin, a critical protein that supports the strength, stability, and function of muscle cells.[3]

Boys are typically diagnosed with DMD between 3 and 5 years old, although symptoms can present in children as young as 2 years old.[4,5] DMD is characterised by progressive impairment of function in all muscles of the body starting at birth, although impairment is typically noticed first in muscles associated with the ability to walk. Boys and young men with DMD typically lose ambulation (the ability to walk) within the first 10–12 years of life, leading to dependency on wheelchair use during the teens to aid mobility. In the later stages of the disease, there are pronounced physical limitations such as complete reliance on a wheelchair and upper limb function limitations become more pronounced, with loss of both shoulder elevation and hand-to-mouth activity from the mid-teens.

Adolescence is usually a time of growing independence and autonomy, but boys and young men with DMD will need their parents to provide increasing help with activities of daily living, including intimate and personal care, as their functional abilities continue to decline.[6] Compared with boys and young men with DMD who are still physically independent, wheelchair dependence, loss of upper limb function, and the ability to swallow all negatively impact health-related quality of life.[7] Loss of hand function is particularly impactful as it prevents participation in most daily activities of adolescence, such as driving an electric wheelchair, eating, schoolwork, computer games and interacting with others on social media; loss of hand function is often considered more difficult than the transition to requiring a wheelchair.[8,9]

Ultimately, DMD leads to premature death, with a life expectancy of 22–28 years.[4,10–13] Boys and young men with DMD are at increased risk of cardiac problems and scoliosis, whereby the spine twists and curves to the side, making it more difficult to breathe, and

eventual early death.[2,3] Heart and lung complications caused by the muscle impairment associated with DMD are the leading causes of death in boys and young men with DMD.[14]

**Number of patients with DMD**

DMD is one of the most common forms of childhood muscular dystrophy, with a worldwide birth incidence of around 1 in 5,050 boys.[15] Cases of DMD in girls are extremely rare, with an estimated rate of 1 case per 50 million births.[16] In the UK, approximately 100 boys are born each year who will be diagnosed with DMD,[17] and there are approximately 529 boys with DMD aged 6 years or over who are able to walk.[18]

**Impact on patients and families/caregivers**

Children with DMD live their whole life with gradually increasing physical impairments and dependency on carers, including parents, siblings, family, and healthcare providers.[5,19] Consequently, DMD has a significant negative impact on a patient's quality of life, which increases as the disease progresses. Losing the ability to walk and dependence on a wheelchair results in a substantial reduction in physical and social activities, which has a significant negative impact on quality of life.[6,19–21] Children with DMD lose the ability to run, jump, and climb which creates a barrier to playing or engaging in sporting activities with friends and siblings.[22] Loss of hand function prevents participation in most daily activities of adolescence, such as driving an electric wheelchair, eating, schoolwork, computer games, and interacting with others on social media and is often considered more difficult than the transition to requiring a wheelchair.[8,9] The inability to engage in these activities and requiring day-to-day assistance leads to a sense of frustration. Feelings of exhaustion due to physical limitations also add to the patient burden.[9]

Most boys and young men require long-term care, which is provided by informal caregivers (such as family members), as well as formal caregivers. This support involves assistance with activities of daily living, such as transfers to a wheelchair, preparing meals, cleaning, dressing, eating, and toileting.[6] Caregivers of people with DMD are at a notable risk of experiencing anxiety, depression, and impaired mental health. Management of DMD is delivered by healthcare providers from a wide range of specialities and involves a huge volume of appointments, which can be logistically complex for families.[6,19,23] The burden for caregivers increases with disease progression, significantly impacting caregivers' overall quality of life, physical, emotional, and mental well-being, as well as their financial and employment status (e.g. difficulty paying bills and missed work hours).[6,19,24,25] Although at its most intense at the time of death of their child, parents experience grief before bereavement and at each disease progression point, such as loss of ambulation, requirement for enteral feeding, and need for non-invasive ventilation.[26]

Negative impacts on quality of life extends beyond parents, with siblings and the wider family also contributing to caregiving duties.[27] Many siblings give up time with friends, sports or extracurricular activities and/or travel, which has a negative impact on their social life and emotion well-being.[28] Ultimately, boys and young men, and their families and caregivers will need to come to terms with the fact that DMD leads to premature death. The loss of a sibling is a highly traumatic event and may be more disruptive than the loss of another family member.[29]

### 2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The diagnosis should be conducted by a neuromuscular specialist who can clinically evaluate the patient.[14,30] If there is a family history of DMD, any suspicion of abnormal muscle function requires testing of serum creatine kinase (CK), an enzyme released by damaged muscles. When there is not a family history of DMD, the following signs of possible DMD indicate that CK testing is necessary: not walking by 16–18 months, Gower's sign, or toe walking. If CK is elevated, confirmation of the diagnosis involves

genetic testing and if necessary, muscle biopsy.[3,30] As givinostat works across all types of DMD genetic mutations, no additional diagnostic tests are required.

### 2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

DMD is a complex disease involving multiple organ systems, and requires management by an extensive multidisciplinary team encompassing healthcare professions from neuromuscular, respiratory, cardiac, orthopaedic, and psychosocial management departments, amongst numerous others.[3] There is no cure for DMD. The goal of treatment is to allow boys and young men with DMD to experience as much of their childhood and early adulthood as possible, by maintaining independence and delaying the time to loss of leg and arm function.[3,31,32]

There are no UK-specific clinical practice guidelines for the management of DMD and UK clinicians typically follow recommendations published by the International DMD Care Considerations working group (last updated in 2018).[3,14,33] DMD Care UK have created 11 working groups of UK experts and patient/caregiver representatives who have been tasked with reviewing international standard standards of care and current UK clinical practice, and developing UK-focused clinical recommendations.[3] To date, bone, endocrine (hormones), cardiac, and respiratory standards of care have been developed;[34] publication of other standards of care is expected in the future.

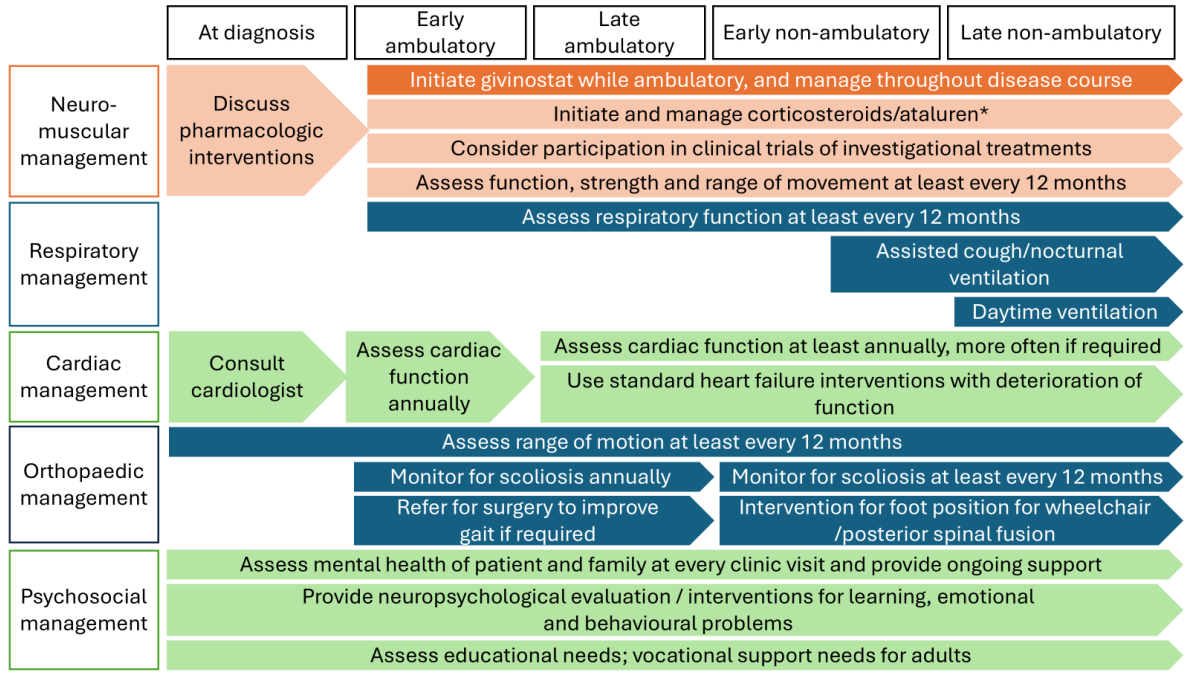
Established clinical management for boys with DMD in England and Wales includes physiotherapy, corticosteroids, and other supportive care (Figure 1).[3]

Boys start taking corticosteroids once the diagnosis of DMD is confirmed, and continue taking them from the early ambulatory phase (5 to 7 years old) through to the late stages of the disease. Corticosteroids, particularly deflazacort and prednisolone help to control symptoms, maintain muscle strength, and delay loss of ambulation. The effectiveness of long-term corticosteroid use is uncertain because adverse events may lead boys and young men to stop taking them. Such adverse events include excessive weight gain, high blood pressure, glucose intolerance, increased risk of bone fractures, and poor mood.[3,35] A modified corticosteroid, vamorolone, has a GB marketing authorisation but is not currently reimbursed by the NHS and is not routinely commissioned by the NHS for DMD.[36]

Ataluren, a drug developed to treat DMD caused by nonsense mutations, was granted conditional marketing authorisation by the European Medicines Agency (EMA) in 2014 for the treatment of ambulatory patients aged 2 years or older with a specific genetic mutation (which occurs in 10–15% of DMD patients).[37] However, the primary endpoint for the pivotal Phase 3 trial was not met. In January 2023, the EMA Committee for Medicinal Products for Human Use (CHMP) recommended non-renewal of the marketing authorisation for ataluren because the new study failed to confirm the drug's effectiveness.[38] Ataluren received a positive NICE recommendation in 2023; it is the only treatment currently recommended by NICE, but only for those with a nonsense mutation in the dystrophin gene. While the MHRA has not yet indicated whether it will follow the EMA and withdraw the marketing approval for ataluren in the UK, its use in clinical practice is expected to decrease in the future as new treatments become available.

Givinostat is positioned as add-on therapy to established clinical management (including corticosteroids) in boys who are ambulant when givinostat treatment is started (Figure 1).

**Figure 1: Current treatment pathway for DMD in England and Wales, and proposed positioning of givinostat**




*Ataluren is indicated and reimbursed only in children aged 2 years and over with a nonsense mutation in the dystrophin gene; however, the CHMP recommended non-renewal of the marketing authorisation for ataluren because the new study failed to confirm its effectiveness

Abbreviations: DMD, Duchenne muscular dystrophy.

Sources: Adapted from Birnkrant DJ, et al. 2018;[3,14] DMD Care UK.[35]

## 2d) Patient-based evidence (PBE) about living with the condition

**Context:**

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

### Patient burden

Duchenne UK published their State of the Nation report in September 2024, which clearly highlights the impact of DMD on boys and young men living with the disease and on those who love and care for them.[19] Two families a week are given the devastating diagnosis that their child has DMD and, in addition to physical disabilities, boys and young men with the disease commonly experience high levels of anxiety, anger, and sleeping problems leading to extreme tiredness. This negatively impacts an affected family's quality of life, specifically impairing parental/carer mental health, relationships with siblings and family outings. The pain and struggle goes largely unnoticed by most of the UK, mainly because DMD is a rare disease.[19]

DMD has a significant impact on the health-related quality of life of boys and young men with the disease; lower scores on a range of quality of life measures are consistently reported when compared with the general population.[20,39] Below is a summary of the results of a study of 46 patient/caregiver pairs, including non-ambulatory boys and young men, which aimed to capture lived experience of the disease, and additional supporting data, some of which was directly sought from patient groups to understand the patient and carer experience.[22]

***Losing lower limb function***

Loss of ambulation is a key milestone in DMD disease progression, typically occurring at 12 years of age, and negatively impacts quality of life.[7]

Boys and caregivers reported difficulties with weakness or lack of strength and most reported tiring easily or lacking energy; approximately half of respondents reported the inability to keep up physically with their peers: "*I would say his physical ability to be outdoors and play with other kids. He can't really play with other kids as I know he would like.*"

These challenges often have a negative emotional impact on the individual living with DMD, as noted by one caregiver: "*I mean not being able to play with his friends – keep up with his friends, and that does upset him sometimes."*

Such physical difficulties also lead to a sense of frustration. One caregiver reported issues with: "*Frustration levels I think recently. Sometimes he almost seems to get down on himself, depressed because of things*."

The future impact of declining mobility is also a concern for younger ambulatory boys. In another study, patients expressed worry and feelings of anxiety when considering the transition to using a wheelchair. One patient stated "*I became self-conscious and worried about how others looked at me. Most likely, they didn't care, but I thought they were looking at me*."[40]

***Losing upper limb function***

The loss of upper limb function leads to severe problems in performing daily activities and participating in society, ultimately affecting independence and quality of life.[41]

Loss of hand function prevents participation in most daily activities of adolescence, such as driving an electric wheelchair, eating, schoolwork, computer games and interacting with others on social media and is often considered more difficult than the transition to requiring a wheelchair.[8,9]

Adolescence is usually a time of growing independence and autonomy, but for boys and young men with DMD, their parents will need to provide increasing assistance with intimate and personal care (e.g. dressing, eating, washing and toileting).[6] One patient stated, "*Losing strength in my arms has limited my independence more than my legs. I find it much harder to do things for myself and it upsets me.*"[42]

For non-ambulatory boys and young men, symptoms and impacts reported were associated with worse upper body function, including difficulties with reaching for objects, wheelchair/bed transfers, fine motor skills such as holding a pencil or turning pages in a book, lifting arms above the head, and lifting objects, which resulted in patients needing additional assistance from caregivers or adaptive devices.

Loss of independence due to physical limitations also has a negative impact on mood. One caregiver reported, "*He just gets frustrated if there's something he can't do that he wants to do. Asking for help sometimes is frustrating for him*."

**<u>Caregiver and family burden</u>**

Caring for a person with DMD is mentally and physically exhausting, time-consuming and has a profound impact on many aspects of daily living. Duties not only include emotional and social support, but also attendance at regular medical and related appointments and the associated time and travel required, home adjustments, impact on parents' ability to work, and admin required to get funding for various aspects of a child's care needs.[6,23] For these reasons, multiple caregivers are involved, both informal (e.g. family and friends network) and formal.

Burden increases with disease progression, significantly impacting caregivers' overall quality of life, physical, emotional, and mental well-being, and employment status.[6,24,25] Caregivers assist young men with wheelchair transfers, help manage daily activities, and

provide support for tasks that become increasingly challenging as the disease progresses. One parent of a son with DMD stated: "*I liken a diagnosis of DMD as death by a thousand cuts. Because for the carers, there is never any "closure". You are given the diagnosis and you never fully come back to your pre-diagnosis mental health state. Instead, you are in state of constant readjustment, stress and anxiety as you watch your son's continual decline. And because the built world is not designed for disabled children and adults EVERYTHING is a struggle."*[42]

Caregivers of boys and young men with DMD are at risk of anxiety, depression, and impaired overall mental health; approximately 50% of caregivers reported being moderately or extremely anxious or depressed, which was significantly higher than the general population, and strongly associated with the health and mental state of the patients (measured by the mental health summary score of the Short Form-12 Health Survey [SF-12]).[6,24] Caregivers' anxiety and depression levels often peak at diagnosis and with each milestone in the patient's disease progression, such as loss of ambulation, requirement of a feeding tube, and need for non-invasive ventilation (i.e. delivery of oxygen via a face mask).[19,26,43] The practical consequences of caregiving results in many caregivers neglecting their hobbies, which may have otherwise provided opportunities for social connection and participation, protective factors against care-related loneliness, stress, anxiety or depression.[44,45] One parent of a son with DMD stated: "*When my son was diagnosed with Duchenne Muscular Dystrophy my mental health hit rock bottom. It has never recovered to pre-diagnosis levels. For the first ten years I was in a profound state of grief. Grieving for the death of a life I thought my son was going to have. And grieving for his short, disabled life. I have now come through that tunnel of grief: and what am I facing? My son is now 17, non-ambulant. I am in constant fear of his heart failing, of his breathing getting worse. And I still grieve every single day for the loss of ambulation, the loss of his arm strength, seeing the devastating impact on his loss of independence, and low feelings of self-esteem.*"[42] Duchenne UK argue strongly that carer health-related quality of life should be included in assessments of new treatments for DMD.[19]

Burden extends beyond the caregivers and parents of boys and young men with DMD. Many siblings give up time with friends, sports or extracurricular activities and/or travel, which has negative impacts on their social life and emotion well-being, which they often feel they have to deal with on their own.[28,46] This can lead to psychological difficulties for siblings, and has a negative impact on their school performance and involvement in leisure activities, and has a further negative impact on their emotional wellbeing (such as being fearful, aggressive, or withdrawn).[27,28]

# SECTION 3: The treatment

### 3a) How does the new treatment work?

What are the important features of this treatment?
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body.
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

**How does givinostat work?**

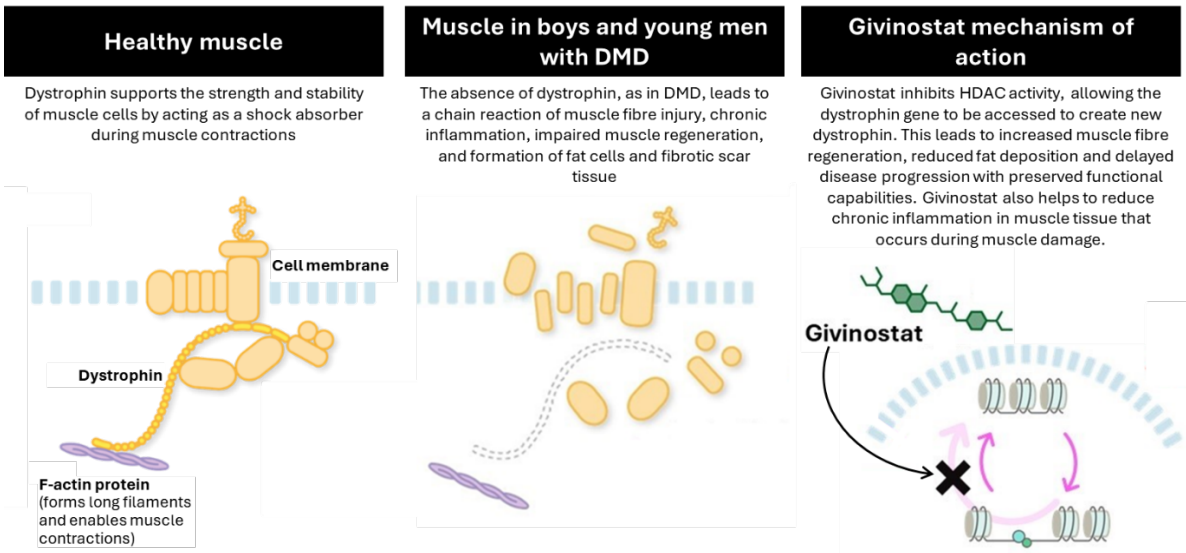
DMD is a progressive neuromuscular disorder caused by a mutation in the dystrophin gene which means the body can't make functional dystrophin, leading to irreversible muscle damage.[1,2,3,47] Dystrophin is a critical protein that supports the strength, stability, and function of muscle cells by acting as a shock absorber to prevent rupture during muscle contraction.[1,2,3,47] Without functional dystrophin, muscle fibres are damaged during contraction. In DMD, the muscle damage is chronic and there are a lack of normal repair processes.[48] This means that fibrotic scar tissue and abnormal fat cells build-up in all muscles in the body, including the heart and lungs.[31,48–50]

These abnormal processes are worsened by the increased levels of histone deacetylases (HDAC) that also occur in DMD.[48] HDACs are enzymes that remove acetyl groups from proteins and influence important processes in the muscle cells.[48] Too much HDAC enzyme activity in DMD means that too many acetyl groups are removed from the histones and that the DNA is too tightly wrapped, which prevents expression of genes and failure to produce specific proteins.[48] Specifically for muscle damage repair this means the immune system is chronically activated and gets 'out of control', and fibro-adipogenic progenitor (FAP) stem cells get stuck in connective tissue production mode instead of supporting the muscle stem cells to differentiate and repair muscle. In addition to histones, other proteins are also regulated by the addition and removal of acetyl groups, which can further exacerbate muscle damage and pathology in DMD.[48]

Givinostat is a novel, non-steroidal, oral HDAC inhibitor (HDACi) with the potential to slow disease progression. By blocking HDAC activity, givinostat prevents the body's immune system from getting over stimulated. This allows muscle repair processes to behave more naturally. Reduced HDAC activity dampens the immune response and prevents extra damage caused by the immune cells, FAP cells don't get stuck in production mode and can return to their supportive role for muscle repair. The FAP cells produce growth factors and activate muscle stem cells, which then transform into new mature muscle fibre and repair the damage.[48,51,52]

Due to its mechanism of action, the effects of givinostat are not limited to specific genetic mutations and it is therefore intended to treat all genetic variants of DMD (Figure 2).

**Figure 2: Givinostat mechanism of action**




Sources: Consalvi S, et al. 2011;49 Kodippili K, Rudnicki MA. 2023;53 Mercuri E, et al. 2024;54 ClinicalTrials.gov. Available at https://clinicaltrials.gov/study/NCT02851797;55 Bettica P, et al. 2016 (suppl);52 Wilson DGS, et al. 2022;56 Campbell KP, Kahl SD. 1989;57 Guiraud S, et al. 2015;58 Reid AL, Alexander MS. 2021;27, Aartsma-Rus A, et al. 2024.48

## Why is givinostat innovative?

Since the introduction of corticosteroids, there haven't been any new therapies that modify the disease course of DMD, and delay disease progression and the associated functional decline. Givinostat has a novel mechanism of action that targets the impact of missing dystrophin by inhibiting HDAC, thereby reducing inflammation, fibre cell injury, and muscle fibrosis while promoting muscle formation (myogenesis).[48,51,52] Consequently, givinostat delays disease progression and preserves functional capabilities for longer in boys and young men with DMD. This mechanism is distinct from gene therapies, the development of which are challenging due to the size of the dystrophin gene, the largest known human

gene. Givinostat is the only HDACi that has been tested in clinical trials in patients with DMD.[48]

Increased HDAC activity and reduced levels of dystrophin occurs in all muscles of boys and young men with DMD. The effects of givinostat are not just limited to lower limbs involved in ambulation, and since HDAC activity is increased in all muscle cells, givinostat works on all genetic variants of DMD.

Givinostat is the first treatment option for boys with DMD that demonstrates clinically meaningful improvements (delays in key measures of functioning for boys and young men with DMD) compared with established clinical management (corticosteroids) studied in one of the largest DMD clinical trials to date.[54,59]

Please refer to the Action Duchenne and World Duchenne websites for more details about the way this treatment works.

### 3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.
If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.
**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**

The proposed place in therapy for givinostat is as an add-on therapy to established clinical management (including corticosteroids) in boys and young men with DMD aged 6 years and older, who can walk (ambulant) when they start givinostat; this includes patients that lose the ability to walk (become non-ambulant) during treatment with givinostat; as shown in Figure 1. Givinostat is not intended to replace corticosteroid use in clinical practice. Both treatments have anti-inflammatory effects, but work through different mechanisms. Corticosteroids reduce inflammation and immune-mediated muscle damage, slowing the degeneration of muscle fibres, while givinostat further reduces inflammation and fibrosis while promoting muscle regeneration.[60] The mechanism of action of givinostat is not anticipated to interact with or otherwise disrupt other therapies used in routine UK clinical practice.

### 3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.
How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dosage of givinostat is based on body weight and the drug is administered twice daily with food. The addition of givinostat to established clinical management (including corticosteroids) is not expected to create additional burden for patents/caregivers.[61]

**Table 1: Recommended dosage of givinostat for patients with DMD aged 6 years or older**

| Actual body weight | Dosage | Oral suspension volume |
|---|---|---|
| 10 kg to <20 kg | 22.2 mg twice daily | 2.5 mL twice daily |
| 20 kg to <40 kg | 31 mg twice daily | 3.5 mL twice daily |
| 40 kg to <60 kg | 44.3 mg twice daily | 5 mL twice daily |
| >60 kg | 53.2 mg twice daily | 6 mL twice daily |

Dosage modifications may be needed for decreased platelet counts, diarrhoea, increased triglycerides, or QTc prolongation (abnormal lengthening of part of the heart's electrical cycle).

### 3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

**Completed studies**

Evidence for givinostat for the treatment of ambulant boys with confirmed DMD aged 6 years or over comes from the Phase 3 EPIDYS (NCT02851797) randomised, double-blind, placebo-controlled clinical trial conducted across 41 specialist hospitals in the UK, the US, Canada, Belgium, France, Germany, Israel, Italy, Netherlands, Serbia, and Spain.[54,59]

The full inclusion and exclusion criteria have been published and can be found in Mercuri E, et al. 2024.[54] Patients in the study were randomly assigned in a 2:1 ratio to receive either givinostat (118 boys) or placebo (61 boys) for 18 weeks, both in addition to established clinical management (corticosteroids). Patients received givinostat or placebo twice daily after a meal.[54,59]

The primary outcome was change from baseline in the four-stair climb (4SC) assessment at 18 months.[54,59] The target population (Group A) included all boys with baseline vastus lateralis (thigh muscle) fat fraction >5% to 30%. This population was used for the prespecified efficacy analyses (120 boys) to ensure a selection of boys who would likely retain ability to walk during the 18-month study period, and to provide the greatest opportunity of making it statistically possible for the study to show a significant treatment difference versus placebo. The overall population (which included all boys who received one or more doses of givinostat or placebo and had usable measurements; also referred to as the safety population) was used for safety evaluations and *post hoc* supportive efficacy analyses (179 boys).[54,59]

Study 43 (NCT01761292) was an open-label (meaning each patient and their physicians knew which treatment they were being given) Phase 2 proof-of-concept study for givinostat to evaluate safety, tolerability, pharmacokinetics, and effects on histology and clinical parameters.[52,62] Study 43 included 20 ambulant boys with DMD aged 7 to <11 years on stable corticosteroid treatment for at least 6 months in Italy.[52,62]

**Ongoing studies**

The open-label study (Study 51; NCT03373968) is an ongoing open-label extension study, which includes patients from both Study 43 and EPIDYS. This study aims to provide longer-term outcomes data for givinostat, as well as evidence of givinostat efficacy in patients that are non-ambulant.[63] The study is expected to complete in December 2025.

The ongoing Phase 3 ULYSSES study (Study 50; NCT05933057) is a randomised, double-blind safety and efficacy study, currently recruiting non-ambulant boys aged between 9 and 17 years. This study will provide further information about the efficacy of givinostat in non-ambulant patients with DMD.[64] Results are not available at the time of this submission, but are expected in mid 2028.

Study 52 is a Phase 2, open-label, safety and pharmacokinetics study in ambulant boys with DMD aged from 2 years to <6 years.[13] The study will follow 18 boys for 12 months with an extension phase up to 24 months.[65] Results are expected in 2028.

### 3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

**EPIDYS primary and secondary endpoints**[54]

*(See company submission, Document B, Section B.2.6)*

***Delays loss of ambulation***

Givinostat slows the progressive decline in muscle function thereby delaying the loss of ambulation, which is an important milestone for boys and young men with DMD.[54,59] This was demonstrated by a meaningful and statistically significant difference in the average change in time to climb four stairs (4SC) compared with placebo (a reduction of approximately 40% in the decline in 4SC over a period of 18 months). This prolonged ability to walk and climb stairs increases the ability to participate in physical and social activities in daily life. More than double the number of boys and young men receiving placebo had 4SC time over 6.2 seconds compared with givinostat, which has previously been shown to predict loss of function in the following year.[54,59]

Results from the 6-minute walking test (6MWT) support the 4SC findings, and add to the evidence that givinostat delays the natural progressive reduction in walking ability compared with placebo.[54,59] The reduction in walking performance was slower with givinostat (−38.20 m) than placebo (−48.86 m).[54,59]

***Delays loss of ability to perform daily activities***

Givinostat has also been shown to maintain the ability of boys and young men with DMD to engage in typical daily activities.[54,59] The North Star Ambulatory Assessment (NSAA) is a scale which measures motor abilities associated with daily activities (e.g. standing and rising, walking and running, stair climbing, balance). NSAA data from EPIDYS were consistent with 4SC results, supporting the role of givinostat in enabling boys and young men with DMD to continue with engage in typical activities of daily living for longer.[54,59] There was evidence to suggest that a decrease in NSAA total score from baseline was lower (i.e. less decline) with givinostat than with placebo. NSAA cumulative loss of function was also numerically lower with givinostat than with placebo (2.14 fewer items failed over 18 months) which is an important finding because it's previously been shown that a loss of 2.0 NSAA items predicted clinically meaningful disease progression and loss of ambulation.[54,59] Both patients and parents perceive deterioration in one or two NSAA items as an important change. Please note, EPIDYS did not include enough boys to provide the statistical power to demonstrate statistically significant differences in the secondary endpoints such as NSAA.[54,59]

***Delays loss of muscle strength***

As lack of dystrophin in DMD results in muscle injury, maintaining muscle strength is a good predictor of retaining functional ability for a longer period. Reductions in both knee extension and elbow flexion muscle strength were numerically less with givinostat than with placebo indicating that givinostat not only helps to maintain the ability to walk by preserving muscle strength in the legs, but also supports the preservation of arm strength which could help maintain their independence (e.g. wheelchair transfers, washing, cleaning) and ability to engage in social activities (e.g. gaming, social media).[54,59] Boys with DMD who received givinostat also had a smaller increase in the time it took them to rise from the floor after 18 months of treatment, compared with boys who received placebo.[54,59] Importantly, a longer time-to-rise from floor (TTRF) can signal a decline in physical capabilities and independence.

***Post hoc analysis of efficacy in the overall EPIDYS population***[66]

The results outlined above are from the target (Group A) EPIDYS population (120 boys), which was used for the efficacy analyses.[54,59] This group was selected based on their

thigh muscle fat fraction to ensure a selection of boys who would likely retain ambulation during the 18 month study period and to provide the greatest opportunity of powering the study to show a significant treatment difference in 4SC in what is a small disease population overall (note, EPIDYS did not include enough boys to provide the statistical power to demonstrate statistically significant differences in the secondary endpoints reported above; all secondary endpoints directionally supported 4SC).[54,59] The wider, overall population (179 boys) was recruited so that the safety of givinostat could be measured in a broader population of boys with DMD.

A supportive analysis of the efficacy of givinostat in the overall population confirmed that the results were consistent with those reported for the Group A population (above).[66] Over the 18-month follow-up period, 4SC decline in the overall population was significantly slower with givinostat than placebo. The key secondary endpoints consistently favoured givinostat over established clinical management which supports the primary endpoint result (4SC).[66]

When running multiple tests, statistical methods need to be used to avoid mistakenly finding a result by chance. After making these adjustments, evidence suggested that givinostat was better than placebo in terms of the decrease in NSAA total score from baseline, cumulative loss of function, and change from baseline in TTRF.[54,59] The lack of statistical significance for the secondary endpoints does not indicate that givinostat was not effective, but rather demonstrates the stringency of the adjustment procedure which does not account for correlations between related endpoints (e.g. thigh fat fraction, which is inversely correlated with muscle function, and therefore, performance on tests such as 4SC and TTRF).[54,59]

***Efficacy data from ongoing the OLE (Study 51; December 2023 data cut)***[67]

The ongoing **Open-label extension (**OLE) study is providing longer-term outcomes for givinostat, including ambulant boys previously treated with givinostat in EPIDYS, ambulant boys who have not previously received givinostat (but were enrolled in Study 43 or EPIDYS), as well as boys and young men from Study 43 and EPIDYS who were non-ambulant at baseline.[67] Data from this study are included in the model because it has longer follow-up than EPIDYS. The mean actual duration of givinostat administration was 1,177 days (range 26 to 2,259 days) as of the latest data cut.[67]

In the ambulant study population, deterioration in muscle function was observed, but data suggest that givinostat delays the occurrence of major disease milestones, including loss of ambulation.[67] Two young men in the givinostat group required daytime respiratory report, but no boys/young men required scoliosis surgery.[67] Two boys/young men had died, but their deaths were due to incidental injury, not due to givinostat treatment.[67]

### 3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?
Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).** Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patient quality of life was measured in EPIDYS using Paediatric Outcomes Data Collection Instrument (PODCI). The PODCI quality of life questionnaire was completed by the boy's parent or the boy himself. A total of five subscales (upper extremity function; transfer and basic mobility; sports and physical functioning; pain/comfort; and happiness) and one global function scale were calculated from the questionnaire.

Givinostat treatment showed a trend towards a reduction in the decline of the health-related quality of life at 18 months when compared with the placebo group, indicating that givinostat treatment does not negatively impact quality of life, and quality of life may decline less rapidly.[54,59]

### 3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer. Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The EPIDYS safety population was used for safety evaluations and comprised all randomly assigned boys who received at least one dose of study drug (i.e. the overall population; 179 boys). Overall, the results demonstrate that boys treated with givinostat show a predictable safety profile consistent with previous studies, with adverse events appearing more frequently in the first 3 months of treatment and manageable through dose management.[54,59] Treatment compliance was high (mean compliance was greater than 98% in both groups), and 95% of boys completed the study. The average treatment duration was 493 days (similar in all treatment groups).[54,59]

Boys received a flexible-dose regimen in EPIDYS, starting with a high dose that was reduced if treatment was not tolerated.[54,59] In the overall population (Groups A and B), approximately 73% of boys in the givinostat group and 46% of boys in the placebo group had dose modifications which were due to adverse events in 46% and 8% of boys, respectively.[54,59]

Similar proportions of boys in both groups had adverse events (95% in the givinostat group and 93% in the placebo group) demonstrating that many of the adverse events were due standard of care (e.g. corticosteroids) that boys in both groups received rather than being related to givinostat treatment.[54,59] Most adverse events in both treatment groups, which both included corticosteroid treatment, were mild to moderate in severity (91% in the givinostat group and 92% in the placebo group).[54,59]

No boys died during the study.[54,59] Overall, eight (7%) boys in the givinostat group and two (3%) boys in the placebo group reported at least one serious adverse event. Serious adverse events in the givinostat group included gastroenteritis, gastroenteritis viral, influenza, abdominal pain, vomiting, chest pain, spinal fracture, dizziness, and rash – all reported by one (1%) boy each. No serious adverse events were considered related to the study drug or led to study withdrawal.[54,59]

Treatment-related adverse events (and adverse events leading to dose reduction) were more common with givinostat than with placebo, although these were typically known to be associated with givinostat treatment (e.g. diarrhoea, low platelet count in the blood, and elevated triglycerides in the blood).[54,59] They appeared more frequently in the first 3 months of treatment and were generally manageable through dose management.[68] None of the severe or serious adverse events were treatment-related or resulted in study withdrawal (see Section 3i below for anticipated monitoring requirements).[54,59]

### 3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

***Lower limb function***

Boys and young men receiving givinostat in EPIDYS retained their ability to walk, hop, jump, run, climb stairs, and rise from a chair or the floor for longer, and therefore, the functional ability to participate in physical and social activities of daily life.[54,59] These improvements in functional abilities are likely due to concomitant improvements in muscle strength (a reduction in DMD-associated decline) of the major leg muscles and a reduction in fat infiltration, which is associated with muscle function and daily activity, and predicts loss of ambulation.[54,59] Loss of ambulation is a significant milestone for patient, caregiver,

and family-member quality of life, therefore, by delaying this, boys and young men with DMD are able to continue playing with friends, engaging in sporting activities, and caring for oneself for longer. This could have a significant impact on their sense of normalcy, self-esteem, anxiety of transitioning to wheelchair, and level of frustration due to not being able to engage social activities.

***Upper limb function***

Given givinostat's mechanism of action (inhibition of HDAC which effects all muscle cells, therefore the effects are not restricted to ambulatory muscles), it is plausible that the positive impact of treatment on lower limbs could extend to upper body function. The loss of independence that comes from upper limb function has a significant impact on quality of life, particularly loss of hand function which is often considered more difficult than the transition to requiring a wheelchair. Givinostat preserved arm strength in EPIDYS (measured by elbow flexion)[54,59] and further data to support this are expected from the ongoing Phase 3 ULYSSES trial which includes upper limb strength as a key outcome. A delay in upper limb functional decline helps boys and young men maintain independence with activities such as wheelchair transfers, eating, washing, and cleaning, which should also have a positive impact on caregiver burden. Furthermore, maintenance of upper limb function is important for adolescents in particular as it will allow them to drive an electric wheelchair, complete schoolwork, play computer games, and interact with others on social media.

***Safety***

EPIDYS safety results demonstrated a predictable and manageable safety profile for givinostat.[54,59] Nearly all boys completed the study, and treatment compliance was high. Similar proportions of boys in both groups had adverse events demonstrating that many of the adverse events were due standard of care (e.g. corticosteroids) that boys in both groups received rather than being related to givinostat treatment. Most adverse events observed with givinostat were mild to moderate in severity, they appeared more frequently in the first 3 months of treatment, and were generally manageable through dose reduction or interruption. No boys died during the study and no severe adverse events were considered related to the study drug or led to withdrawal from the study.[54,59]

***Quality of life***

Reflecting the slower progression of disease for boys and young men who received givinostat, there was a trend towards a reduction in the decline of the quality of life for DMD boys over time with givinostat, when compared with the placebo group, which was likely driven by the maintenance of functional abilities due to delayed decline ambulation and muscle strength.[54,59]

***Administration burden***

Since givinostat is an oral treatment, there isn't expected to be any additional administration burden when combined with corticosteroid treatment, which is also taken orally.

**3i) Summary of key disadvantages of treatment for patients**

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Givinostat is an efficacious and well-tolerated treatment. Known side effects of givinostat treatment, such as diarrhoea, elevated blood triglycerides, and decreased platelet count, were more common with givinostat compared with placebo in the EPIDYS study.[54,59]These adverse events were generally manageable through temporary dose reduction or interruption.[54,59]

On givinostat treatment, anticipated monitoring requirements are that blood counts should be monitored every 2 weeks for the first 2 months of treatment, at month 3 and every 3 months thereafter, and triglycerides should be monitored at 1 month, 3 months, 6 months, and then every 6 months thereafter. This monitoring schedule is more frequent than every 6 to 12 months as is typical with corticosteroid use.[69]

### 3j) Value and economic considerations

**Introduction for patients:**
Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.
In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

**Cost-effectiveness assessment of new medicines**

In assessing whether a medicine represents a cost-effective use of NHS resources, NICE refers to a measure called the incremental cost-effectiveness ratio (ICER).[70] This looks at the cost-effectiveness of the product in question – in this case, givinostat – against other treatments currently used to treat DMD – in this case, established clinical management (ECM). The ICER is calculated as the difference between the total costs accrued in the ECM arm and the givinostat arm, divided by the difference between the total QALYs accrued in the ECM arm and the givinostat arm. The QALY is a measure of disease burden and includes both the quality and quantity of life lived.

This submission utilises the output from Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis), a unique initiative, led by Duchenne UK, to develop tools and evidence to support HTA and reimbursement decisions for new treatments for DMD. One of the key outputs from this initiative is the development of a cost-effectiveness model (CEM).

The CEM predicts the movement of patients between disease health states and death across a patient's lifetime for: (1) patients receiving established clinical management (ECM) and (2) patients receiving givinostat in addition to ECM. The disease health states included in the CEM are ambulatory and non-ambulatory health states, plus an intermediate "transfer" health state, and death.

Movement between disease health states and death over time is informed by UK real-world evidence for ECM. For givinostat, whilst the EPIDYS clinical trial provides head-to-head data comparing givinostat to ECM for 18-months and the OLE study (Study 51) provides ongoing data on givinostat, there are no head-to-head data comparing givinostat to ECM for outcomes informing the CEM i.e., loss of ambulation, hand-to-mouth function, and lung function. Note: whilst the EPIDYS clinical trial collected data on these outcomes, there were either few or no events observed within the 18-month follow-up. Therefore, the CEM relies on information from an indirect treatment comparison (ITC), conducted using the data from the OLE study for givinostat and the UK real-world evidence for ECM.

Costs and QALYs are accumulated in each health state and summed within each treatment arm. Four broad categories of healthcare costs are included in the CEM, including therapy-related costs, health-state costs, comorbidity costs, and treatment-related AE costs. QALYs are considered for the patient and two caregivers.

Caregiver QALYs are highly relevant to this decision problem - because of the devastating disease progression, patients with DMD inevitably transition towards a state of total dependency, requiring wheelchairs for mobility from their early teens and ventilation support for survival in more advanced stages of the disease. Many patients with DMD also suffer from mental health comorbidities, such as autism spectrum disorder and obsessive-compulsive disorder. Therefore, patients progress to requiring 24-hour care, often provided by informal caregivers. Providing this level of care has a detrimental effect on the mental and physical health of caregivers, as well as on their day-to-day activities and professional life, which worsens as the disease progresses.

**Cost-effectiveness analysis for givinostat**

Givinostat increases the amount of time spent in earlier disease health states i.e., delays the time to key disease milestones in comparison to ECM, and is predicted to increase the overall amount of time spent alive by ultimately delaying disease progression.

Additional value of givinostat is shown in the economic model by reducing the cost and quality-of-life burden of full-time ventilation and spinal fusion surgery. These savings are driven by givinostat prolonging the time to reach full-time ventilation compared with ECM alone and a lower rate of scoliosis requiring spinal fusion surgery. This means that, although the total treatment cost associated with givinostat is greater than ECM, the length of life and quality of life benefit (i.e., total QALYs) are also greater, and full-time ventilation and spinal fusion surgery costs are reduced.

### 3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Since the introduction of corticosteroids, there haven't been any new therapies that modify the disease course of DMD, and delay disease progression and loss of ambulation. Furthermore, use of ataluren is expected to decrease because the latest data failed to confirm the drug's effectiveness.[38] Givinostat has a novel mechanism of action and is the first treatment option for boys with DMD that demonstrates clinically meaningful and statistically significant improvements in functional primary endpoints for DMD patients compared with established clinical management studied in one of the largest DMD clinical trials to date. Due to the mechanism of action, givinostat is intended to treat all genetic variants of DMD and may work on all muscles, not just lower limbs.

**Benefits not captured in the QALY**

Caregiver burden in DMD is substantial, as described above. The quality of life impact for two caregivers – e.g. two parents – while a boy or young man with DMD is alive is estimated in the economic model for givinostat. In reality, this is likely to substantially underestimate the impact of DMD on caregivers, and the wider societal impact of DMD is not fully captured by the QALY. Negative impacts on quality of life extends beyond two parents, with siblings and the wider family also contributing to caregiving duties and being impacted by the disease.[27] Many siblings give up time with friends, sports or extracurricular activities and/or travel, which has negative impacts on their social life and emotional wellbeing, which they often feel they have to deal with on their own.[28,46] Furthermore, the loss of a sibling is a highly traumatic event and may be more disruptive than the loss of another family member.[29] The fact that the economic model is only able to account for quality of life impact while boys and young men are alive will further underestimate the burden of this debilitating disease, which is likely to persist in some form for the family members left behind once boys and young men with DMD die. These additional impacts are substantial, and should be taken into account when considering the evaluation of givinostat for boys with DMD.

### 3l) Equalities

| Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.<br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here |
|---|
| DMD affects both children and young adults. Age is protected under the equality act. Therefore, any difference in access to treatment on the basis of age may raise potential equality issues.<br><br>DMD affects mostly boys, although presentations in girls can occur but are rare. Sex is a protected characteristics under the equalities act. Therefore, any differences in access to treatment on the basis of sex may raise potential equality issues. Further studies are needed to establish the possible effect of givinostat on girls and young women with DMD.<br><br>Many boys and young men with DMD have mobility difficulties or use adaptive equipment or assistive devices such as manual or power wheelchairs, and they have accessibility needs. Given the level of disability boys and young men with DMD experience, restrictions on the centres able to prescribe or administer givinostat may raise concerns about travel accessibility and duration.<br><br>A significant proportion of people with DMD have poor outcomes because of learning or behavioural difficulties, ADHD, autism, and pre-existing psychiatric difficulties.[19] A significant proportion of people with DMD cannot have corticosteroids because of these issues and have worse outcomes. |

## SECTION 4: Further information, glossary and references

### 4a) Further information

| Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access. |
|---|
| **Information related to DMD:**<br>• Muscular Dystrophy Association<br>• Muscular Dystrophy UK<br>• Action Duchenne<br>• Duchenne UK<br>• DMD Care UK<br>• NHS<br>• DMD Care Considerations guidelines (2018) – Part 1 \| Part 2 \| Part 3<br>**Key published EPIDYS clinical trial data:**<br>• Mercuri E, et al. 2024<br>**Givinostat**<br>• USPI<br>**Related National Policy documents:**<br>• The NHS Long Term Plan (2019)<br>• NHS England (2017) - NHS Medicines for Children's Policy<br>• Department of Health and Social Care (2016) NHS outcomes framework 2016 to 2017<br>• NHS Digital (2022) NHS Outcomes Framework England, March 2022 Annual Publication<br>• NHS England (2023) Manual for prescribed specialist services (2023/2024)<br>**Further information:** |

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment – an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

### 4b) Glossary of terms

**Dystrophin** – a structural protein which plays a crucial role in maintaining the structural integrity of the muscle cell fibre membrane

**Histone** – a basic protein found in DNA

**Histone deacetylase (HDAC)** – enzymes involved in turning off gene activities which affect the ability of muscle cells to regenerate; givinostat is an inhibitor of HDAC

**ICER** – incremental cost-effectiveness ratio. Measure of the cost-effectiveness of a medicine against other treatments currently used to treat the condition.

**Licensed medicine** – a drug that has been assessed for efficacy, safety, and quality, has been manufactured to appropriate quality standards, and, when placed on the market, is accompanied by appropriate product information and labelling, that is, it has been authorised for marketing.

**Marketing authorisation** – permission to sell a medicine after the evidence around it (on safety, quality, and efficacy) has been assessed. This is different from NICE's appraisal of a medicine, which also considers whether the medicine is cost-effective for the NHS.

**Open-label trial** – a trial where patients and physicians have knowledge of the assigned treatment.

**Phase 3** – a clinical study that investigates how safe and efficacious a medicine is. The medicine will previously have been tested in Phase 1–2 studies, which test whether the medicine is safe enough to use in humans and has an effect on the disease.

**QALY** – quality-adjusted life year. A measure of disease burden, including both the quality and quantity of life lived, used for the economic assessment of medicines.

**Randomised trial** – a study in which a number of similar patients are randomly assigned to two (or more) groups to test a specific drug or other intervention (e.g., a group being given the medicine or a group being given a comparator).

### 4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:


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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

## Responses to Clarification questions

## 23 January 2025

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6323 givinostat _Company-response-to-CQs_[REDACTED] | 1.0 | No | 23/01/2025 |

# Section A: Clarification on effectiveness data

## *Company's clinical trials and studies*

**A1. <u>Priority question</u>: In the EPIDYS study, 15% of participants in the givinostat and 11% in the placebo arm (overall ITT population) had a point mutation. Of these participants, how many would have been eligible for ataluren?**

**Response:** In the EPIDYS Group A (Target intention-to-treat [ITT]) population, there were 10 patients in the givinostat group and 2 patients in the established clinical management (ECM) group with a point mutation.[1] In the Overall EPIDYS ITT population, there were 18 patients in the givinostat group and 7 patients in the ECM group with a point mutation. The Company does not have data for the percentage of these point mutations that were nonsense mutations in EPIDYS, so do not know how many of the patients in the trial would have been eligible for ataluren.

Ataluren was excluded in the EPIDYS trial to avoid confounding of the results. The exclusion criteria listed in the Company submission (CS) Appendix M1.2 include 'Have exposure to any dystrophin restoration product (e.g., Ataluren, Exon-skipping) within 6 months prior to the start of study treatment', and ataluren was not permitted during EPIDYS.[2,3]

Notwithstanding the data presented above, the Company does not consider ataluren an appropriate comparator for givinostat in this appraisal. The use of ataluren in routine clinical practice for people aged 2 years and older with Duchenne muscular dystrophy (DMD) who have a mutation in the dystrophin gene, a small subgroup of the DMD population, is anticipated to decline following regulatory reappraisal in Europe, which has questioned efficacy within its license.[4–6] Having concluded that the totality of the evidence shows a negative benefit-risk balance, the European Medicines Agency (EMA) recommended in June 2024 that the marketing authorisation for ataluren should not be renewed.[7] The Company is not aware of any information in the public domain about a reappraisal of ataluren by the Medicines and Healthcare Products Regulatory Agency (MHRA) but considers that given the significant uncertainty in terms of its efficacy, future access to ataluren, and therefore use as part

of routine National Health Service (NHS) clinical practice for the treatment of DMD, is highly uncertain. Further, the NICE appraisal of ataluren followed the HST route.[8]

**A2. <u>Priority question:</u> Participants in EPIDYS and Study 43 are described as 'ambulant'. Please can you clarify the criteria or test thresholds used for defining 'ambulant' in EPIDYS and Study 43?**

**Response:** EPIDYS was designed to assess the effects of givinostat on disease progression over 18 months versus established clinical management (ECM) in ambulant patients with DMD.[2] Therefore the inclusion criteria for the EPIDYS Target ITT (Group A) population were chosen with the intention of selecting boys who were not at risk of sudden, complete loss of ambulation but who, if receiving placebo, would show sufficient decline over the study duration in the function, strength, and fat fraction endpoints being tested.[2,3] The relevant EPIDYS inclusion criteria for defining boys as 'ambulatory' were the mean of two screening 4-stair climb (4SC) assessments of ≤8 seconds (results of the two 4SC screening tests must have been within ±1 second of each other), and time to rise from the floor of between ≥3 and <10 seconds at screening.[2,3] The EPIDYS inclusion criteria were based on expert opinion and are consistent with the recommendations of a 2017 consensus workshop by the DMD outcome measure study group.[9] The overall results of EPIDYS showed that givinostat significantly slowed the rate of disease progression and showed less decline in muscle function for boys with DMD over 18 months of treatment versus ECM.[2,3]

The inclusion and exclusion criteria for Study 43 were selected to ensure an adequate assessment of givinostat safety, efficacy, and PK parameters in the study, and considering the expected mechanism of action of givinostat in DMD.[10] The relevant inclusion criteria for defining included boys as 'ambulatory', was that boys were able to complete two screening six-minute walking tests (6MWTs) with a minimal distance of at least 250 metres each (the results of these two tests must have been within ±30 metres of each other).[10]

**A3.** OLE Population: Please can you provide the number of participants in each arm by disease stage (e.g. "early ambulatory", "late ambulatory", "early non- ambulatory") at the commencement of the OLE study?

**Response:** The EAG confirmed in the CQ clarification call that there are no consensus definitions of the early/late ambulatory and of early/late non-ambulatory patients.

The company is therefore unable to analyse the data in the way requested, but we can provide data by ambulatory versus non-ambulatory status (see Table 1 below) and a qualitative description of the study populations.

The Open-label extension (OLE) study definition of non-ambulant is a patient who is unable to complete the 10 metre walk/run in 30 seconds or less without any support or devices.[11] Table 1 presents the available baseline data for the patients in the OLE study as of Dec 2023 DCO.[11] At OLE enrolment, the mean overall time since DMD diagnosis was 7.4 years, and almost all patients (94.2%) were able to walk/run 10 metres in ≤30 seconds.[11]

**Table 1: Baseline data from the ongoing OLE study (Study 51)**

| N at study entry | Givinostat | Delayed givinostat | Naïve givinostat |
|---|---|---|---|
| Total | 119 | 58 | 30 |
| Ambulatory | 110 | 55 | 30 |
| Non-ambulatory<br>Time since diagnosis | 9<br>7.57 (2.541) | 3<br>7.25 (2.734) | 0<br>6.92 (2.737) |

Abbreviations: OLE, Open-label extension.
Source: DoF (Study 51 Clinical Study Report; Dec 2023 DCO).[11]

**A4. <u>Priority question:</u> In the EPIDYS study, the baseline and follow up values for the givinostat arm are only reported for Group A and placebo, and not for Group B. Some baseline values are also not available for Group A, or the overall population. Please can the company provide the following baseline and follow up values for Group B, and for Group A and placebo? Please also note question A8 below.**

**Response:** The baseline data that the Company can provide for Group B is included in Table 2 below, together with the primary endpoint (4SC) results for Group B (which is currently confidential but is due for publication at the end of March 2025).

Primary outcome data for Group B show that although the patient numbers for Group B are small, the primary endpoint results [redacted] the results for the Group A (Target ITT) and Overall ITT populations (see CQ reponse A8).

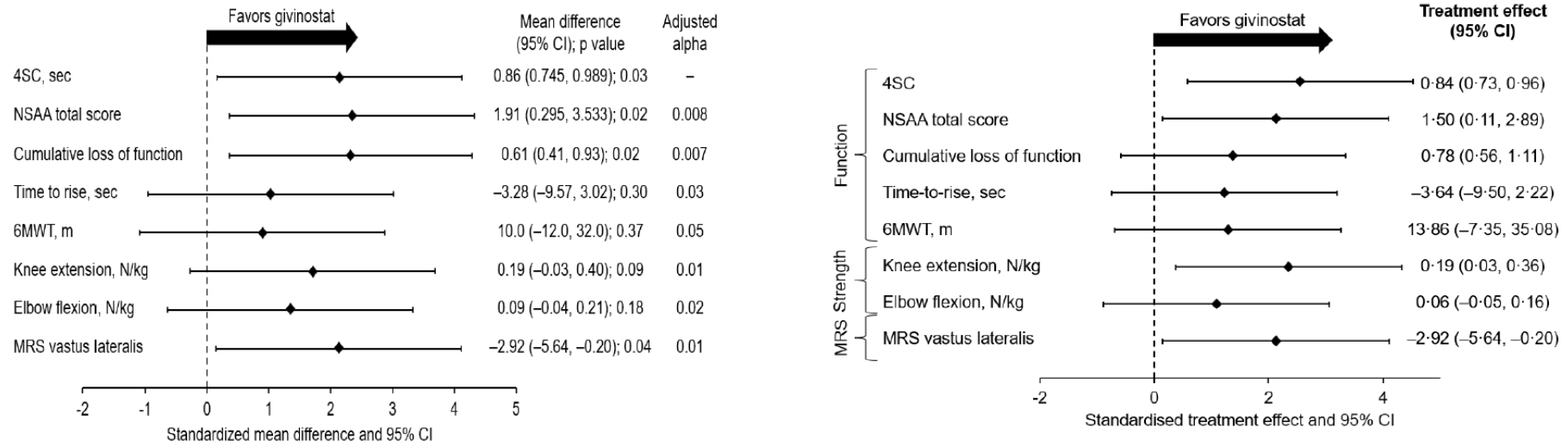
Data for the secondary endpoints are not available for Group B. However, the secondary outcome results in the Overall population were consistent with those in the Group A (Target ITT) population, showing that the Group B population did not affect the overall study conclusions.[2,3,12] The results of a *post hoc* analysis performed to evaluate the effect of givinostat compared with established clinical management in the Overall ITT population on both the primary endpoint (4SC) and six key secondary endpoints of givinostat efficacy are presented in see Figure 1 below and in Section B.2.6.4 of the CS.[12]

The requested patient outcomes at baseline and 18 months for the Group A (Target ITT) population are presented in Table 3 below.

**Table 2: EPIDYS Group B data requested by the EAG**

| Characteristic | Givinostat (Group B) | |
|---|---|---|
| | n=37 | |
| | Baseline | 18 months (end of study) |
| Age, years (mean [SD]) | 10.1 (2.3) | Not available |
| BMI, kg/m$^2$ (mean [SD]: range) | 20.2 (4.6): 13.9–30.3 | Not available |
| Weight, kg (mean [SD]) | 33.5 (11.6) | Not available |
| Time since diagnosis, years (mean [SD]) | 4.9 (2.7) | Not available |
| Time since corticosteroid initiation (years) (mean [SD]) | 3.4 (2.2) | Not available |
| Total NSAA score (mean [SD]) | [redacted] | Not available |
| 4SC, seconds (mean [SD]) | [redacted] | [redacted] |
| 4SC (median [IQR]) | [redacted] | Not available |
| Time to rise (mean [SD]) | Not available | Not available |
| VL MFF (mean [SD]) | Not available | Not available |
| VL MFF (median [IQR]) | Not available | Not available |
| Time to run/walk 10 metres (mean [SD]) | Not available | Not available |
| Distance walked in 6 minutes (mean [SD]) | Not available | Not available |

**Figure 1: Forest plot primary and key secondary endpoints at Month 18 | Group A (Target ITT) population (left hand plot) compared with Overall ITT population (right hand plot)**




Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walking test; CI, confidence interval; ITT; intention-to-treat; MRS, magnetic resonance spectroscopy; NSAA, North Star Ambulatory Assessment.
Source: Mercuri et al. 2024 (poster presented at MDA 2024).[12]

**Table 3: EPIDYS study data requested by EAG | Patient outcomes (Group A ITT population)**

| | Givinostat Group A (Target ITT) population | | Placebo | |
|---|---|---|---|---|
| **Characteristic** | **Baseline** | **18 months (end of study)** | **Baseline** | **18 months (end of study)** |
| | **n=81** | | **n=39** | |
| Total NSAA score (mean [SD]) | 24.44 [5.09] | 21.89 [6.48] | 24.67 [4.79] | 19.87[6.97] |
| Time to rise, seconds (mean [SD]) | 5.57 [1.86] | 14.43 [18.64] | 5.59 [1.96] | 19.17 [21.52] |
| Time to run/walk 10 metres, seconds (mean [SD]) | 5.41 [1.24] | 6.04 [1.97] | 5.18 [0.95] | 7.99 [8.76] |
| Distance walked in 6 minutes, metres (mean [SD]) | 403.31 [72.11] | 365.11 [81.08] | 399.64 [63.83] | 350.78 [91.25] |
| | **n=77** | | **n=37** | |
| VL MFF assessed by MRS, % (mean [SD]) | 15.45 [6.37] | 22.93 [10.36] | 15.95 [6.66] | 26.84 [12.03] |
| VL MFF assessed by MRS, % (median [IQR; Q1, Q3)]) | 15.00 [10.00, 21.00] | 23.00 [14.00, 29.00] | 15.00 [10.00, 20.00] | 26.00 [16.00, 37.00] |

Abbreviations: IQR, interquartile range; MRS, Magnetic resonance spectroscopy; NSAA, North Star Ambulatory Assessment; SD, standard deviation; VL MFF, Vastus lateralis muscle fat fraction.
Source: DoF EPIDYS CSR (tables and figures)[13]

**A5. <u>Priority question:</u> Tables are referred to within the EPIDYS CSR that do not appear to be provided within the CSR (e.g. table 14.3.9.2.2). Please can you confirm if there is an Appendix to the CSR and if so, please can you provide the EAG with this Appendix?**

**Response:** Thank you for flagging. We have enclosed Section 14 (CSR Tables and Figures) with this response document.

**A6. <u>Priority question</u> EPIDYS population: What proportion of participants by arm and group (A and B separately) were recruited to the study pre- and post-protocol changes for dose?**

**Response:** In the Group A (Target ITT) population, 58 patients were recruited to EPIDYS before the protocol change for dose. In the Group B population, 24 patients were recruited before this protocol change. The information by treatment arm is provided in Table 4 below. The distribution of the patient numbers across the treatment arms closely reflects the overall 2:1 randomisation ratio for givinostat versus placebo, showing high internal consistency of these sub-groups with the rest of the EPIDYS study.

As explained in Section B.2.6.1 of the CS (page 79), the *post hoc* analysis of covariance (ANCOVA) suggested that the treatment effect was not affected by the change in treatment regimen (see also Appendix E.2.1 of CS).

**Table 4: EPIDYS | patients recruited pre- and post-protocol changes for dose**

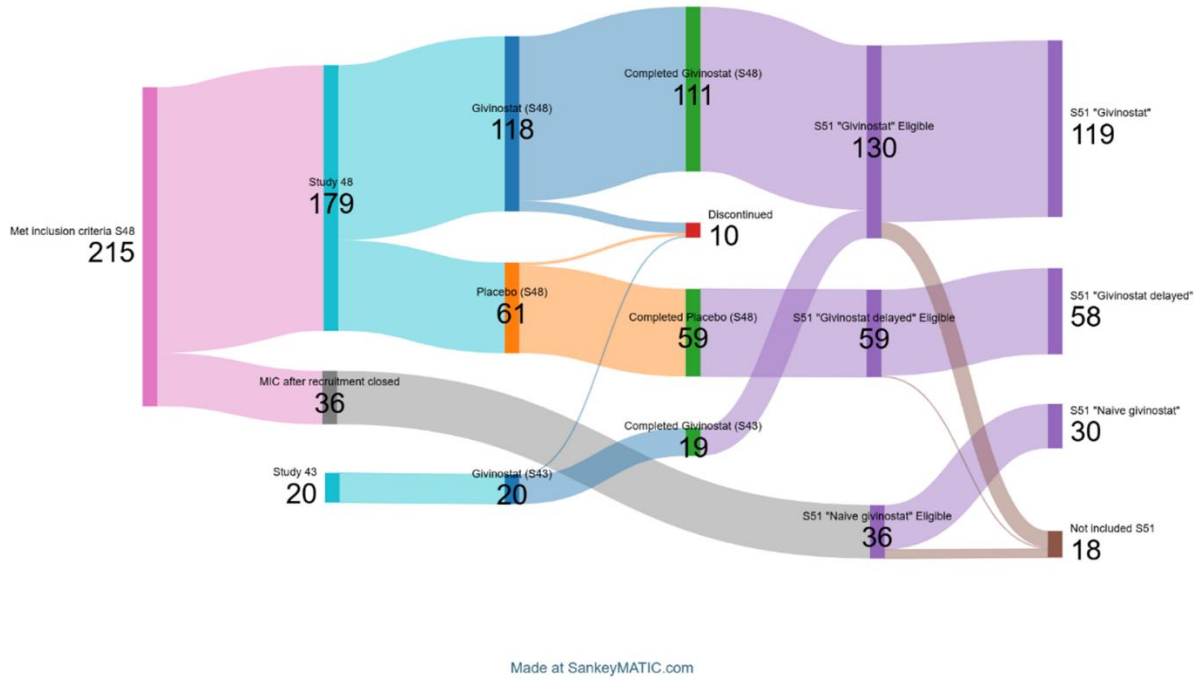
| | | Pre protocol change for starting dose (Until protocol version 4.0) | Post protocol change for starting dose (after protocol version 4.0) |
|---|---|---|---|
| **Group A (Target ITT) population** | Givinostat | 39 | 42 |
| | Placebo | 19 | 20 |
| | **TOTAL** | **58** | **62** |
| **Group B (Off-target) population** | Givinostat | 16 | 21 |
| | Placebo | 8 | 14 |
| | **TOTAL** | **24** | **35** |
| **Overall ITT population** | Givinostat | 55 | 63 |
| | Placebo | 27 | 34 |
| | **TOTAL** | **82** | **97** |

Abbreviations: ITT, intention-to-treat.
Source: DoF EPIDYS CSR;[1] DoF EPIDYS CSR (tables and figures)[13]

**A7. <u>Priority question:</u> Please can you confirm that the participant flow diagram we have presented below accurately describes the flow through the studies included in the company's submission? (Larger version provided at end of document on page 19)**

**Response:** The Company agrees with the figures in the EAG's participant flow diagram (Figure 2). As the OLE (Study 51) was still open as of the fifth interim analysis (IA5, DCO 31 Dec 2023) to enable patients who complete future givinostat studies to eventually join the OLE, the 18 patients (number in brown in the diagram below) applies to the OLE IA5 baseline.[11]

**Figure 2: OLE participant flow diagram (as of baseline for IA5, DCO 31 Dec 2023)**




Abbreviations: DCO, data cut off, IA5, 5th interim analysis; MIC, met inclusion criteria; OLE, Open-label extension, S43, Study 43; S48, EPIDYS (Study 48); S51, OLE (Study 51).
Sources: Mercuri et al. 2024;[2,3] Bettica et al. 2016;[10] DoF (Study 51 Clinical Study Report; Dec 2023 DCO).[11]

**A8. <u>Priority question:</u> EPIDYS results: The company submission document only reports the results of group A (the target ITT) analysis or the combined group A and B (overall ITT). Could the company also provide the mean change from baseline results for the primary and secondary outcomes for group B of the givinostat arm of EPIDYS separately?**

**Response:** The data requested are available for the primary endpoint only. In the Group B (Off-target) population, the baseline 4SC mean (SD) time was [redacted]

seconds in the givinostat group (n=37) and [redacted] seconds in the ECM group (n=22), compared with 3.4 (1.1) and 3.5 (1.3) seconds, respectively in the Group A (Target ITT) population. The [redacted] baseline 4SC time in Group B suggests a more [redacted]. At Month 18, the 4SC mean (SD) time was [redacted] and [redacted] seconds in the Group B givinostat and ECM groups, respectively, and 4.7 (3.2) and 6.4 (7.7) seconds in Group A. Although the Group B subgroup was not powered to detect a statistically significant difference, the least-squares mean difference relative to placebo indicated a [redacted] seconds [redacted] with givinostat. In Group A, a 1.78 seconds smaller decline was observed for givinostat relative to placebo (p=0.037). These data are confidential until publication, expected at the end of March 2025.

In conclusion, although the patient numbers for Group B are small, the primary endpoint results [redacted] the results for the Group A (Target ITT) and Overall ITT populations.

As can been seen in Figure 1 in this document, the outcome results for the secondary endpoint in the Overall population were consistent with those in the Group A (Target ITT) population, showing that the Group B population did not affect the overall study conclusions.2,3,12

**A9.** Figure 10 (page 42 of CS, Doc B): inclusion in EPIDYS required participants to have received stable systemic corticosteroids for 6 months prior to commencement of the study, and for there to be a reasonable expectation of no further dose adjustments. Please could the company clarify whether the proposed place in therapy for givinostat is for it to be started at the same time as corticosteroids?

**Response:** In line with the givinostat Summary of Product Characteristics (SPC), givinostat can be given with or without systemic corticosteroids, according to the discretion of the prescribing physician, to patients with DMD 6 years of age and older.[14] The proposed place in therapy of givinostat is not related to the use, timing or dosages of systemic corticosteroids. However, in clinical practice, systemic corticosteroids are typically started earlier than age 6 (which is the earliest givinostat can be given), once the diagnosis of DMD is established, so the Company does not anticipate that givinostat will be started at the same time as systemic corticosteroid initiation.

EPIDYS required participants to have received stable systemic corticosteroids for 6 months prior to commencement of the study (with a reasonable expectation that corticosteroid dose and regimen would not change over the duration of the study) to ensure that the givinostat outcomes were not confounded by changes in corticosteroid use.[2,3]

**A10. <u>Priority question:</u> Figure 10 (page 42 of CS, Doc B) appears to suggest that patients who are eligible to receive atularen should start both atularen and givinostat. Please could the company confirm this is correct? If so, can you include evidence on clinical effectiveness for this population comparing atularen + givinostat + vs atularen.**

**Response:** The Company apologises for giving that impression in Figure 10 of the CS. The use of ataluren with givinostat is not contraindicated in the Summary of Product Characteristics (SPC) nor is it listed as known interactions with givinostat.[14] It would be at the discretion and responsibility of the prescribing physician to treat with ataluren during treatment with givinostat.

Givinostat has not been studied in combination with ataluren. In the EPIDYS pivotal Phase III trial and OLE, one of the exclusion criteria included having exposure to any dystrophin restoration product (e.g., Ataluren, exon-skipping) within 6 months prior to the start of study treatment (see CS Appendix M1.2).[2,3] Prohibited concomitant medications also included 'any dystrophin restoration product' (e.g. Ataluren) in both the EPIDYS and OLE studies .

As stated on page 10 of the CS, the Company does not consider ataluren to be an appropriate comparator for givinostat in this population. Further, the Company believes that there is significant uncertainty around the efficacy of ataluren, and that its future use as part of routine National Health Service (NHS) clinical practice for the treatment of DMD is highly uncertain. The EMA recommended in June 2024 that the marketing authorisation for ataluren should not be renewed, following regulatory reappraisal.[7] Therefore, while givinostat and ataluren can be given together in theory, this is unlikely for the reasons above.

**A11. <u>Priority question:</u> Please can the company provide the definition of 'established clinical management' used in the EPIDYS trial?**

**Response:** EPIDYS was designed to assess the effects of givinostat on disease progression over 18 months versus current management (which includes systemic corticosteroids, and surgical, and rehabilitative interventions) in ambulant patients with DMD.[2] While givinostat is intended for use by physicians in addition to their usual clinical practice (in line with the licenced indications/contraindication/warning and precautions described in the SPC),[14] the established clinical management criteria used in EPIDYS were to ensure that the givinostat outcomes were not confounded by other therapies. The EPIDYS definition of established clinical management is therefore based on the study inclusions, exclusions and concomitant medicine rules, as described in the CS Appendix M1.1, M.1.2 and Table 11 of Document B.

In essence, EPIDYS established clinical management included stable systemic corticosteroids (for at least 6 months before givinostat treatment and with a reasonable expectation that corticosteroid dose and regimen would not change over the duration of the study); and excluded (prior to and during the study) investigational drugs, dystrophin restoration products (e.g., ataluren), any pharmacologic treatment (e.g., growth hormone) that might have an effect on muscle strength or function (other than corticosteroids), and surgery that might have an effect on muscle strength or function, or change in contracture treatment (either of these within 3 months before study entry or planned/expected to be needed during the study).[2,3] Established clinical management could include stable doses of Vitamin D, calcium, and any other supplements - if clinically indicated before enrolment and for duration of EPIDYS. Medication to treat minor treatment-emergent illnesses were generally permitted, as were supportive treatments (e.g., anti-emetics, anti-diarrhoeals, anti-pyretics, anti-allergics, analgesics, and antibiotics). Testosterone was also allowed if it was used as a replacement therapy for the treatment of delayed puberty, and testosterone dose and regimen was stable for at least 6 months before givinostat treatment and circulating testosterone levels were within the normal ranges for the patient's age.[2,3]

**A12.** The company state that the EMA recommend the four stair climb (4SC) as an outcome. The EAG cannot find this statement referenced in the EMA's guidelines, please could you provide the citation that supports the choice of outcome for the EPIDYS?

**Response:** EMA recommendations state (page 8)[15] that "two endpoints should be selected from the domains muscle strength (depending on the functional status and the compound tested) and motor function. According to the motor system parameter estimated to be particularly affected, one should be selected as primary endpoint and the other as secondary endpoint". Furthermore, EMA recommendations underline (page 9) that, "timed function tests continue to be used clinically and in study programmes because they provide relevant information".[15,16]

As per the recommendations outlined in the EMA Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy[15] and in the FDA Guidance for Industry: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment (FDA 2018),[17] functional improvement or at least delay of progression and deterioration is considered the most relevant outcome measure for patients affected by DMD.

Therefore, the EPIDYS study is fully consistent with EMA recommendations, with 4SC being a time function test used as the primary endpoint to evaluate muscle strength and motor function.

From a patient perspective, 4SC is a clinically meaningful endpoint, as slower 4SC correlates with reduced participation in physical and social activities in daily life and predicts loss of stair-climbing ability and ambulatory capacity.[18] 4SC is also highly correlated with knee extension strength, and the duration of 4SC affects the HRQoL measure of PODCI (with higher baseline 4SC leading to greater declines.[18–21]

**A13. <u>Priority question:</u> The SAP for EPIDYS states that "*The need for a possible log transformation of these variables will be investigated prior to unblinding by assessing the ANCOVA model residuals without a treatment term"* (page 28). In Doc B of the CS, only the primary effectiveness outcome (4SC) has been transformed. Please can the company explain why analyses for the secondary outcome data were not conducted on log-transformed data?**

**Response:** Before unblinding the data, the Sponsor assessed the possible need for log transformation of the primary and secondary efficacy variables by evaluation of ANCOVA model residuals without a treatment effect term. Based on the evaluation of the variables distribution, log transformation was not deemed to be required for the secondary endpoints.

## *Questions on the Matching Adjusted Indirect Comparison*

**A14. <u>Priority question:</u> The CS states results from the OLE study (study 51) were used for the ITC analysis, but also state "patients who were randomised to placebo in EPIDYS and who received delayed givinostat in the OLE study were excluded". Additionally, "patients who were enrolled in Study 51 but were previously enrolled in Study 43 were excluded due to different inclusion/exclusion criteria and givinostat exposure in Study 43 and EPIDYS.**

**Can you clarify if the data presented in the CSR (baseline and results) excludes these patients. If not, can you share the baseline data and results for the patients that were included in the ITC only? Can you also clarify if the naïve givinostat group from study 51 was included in the ITC**

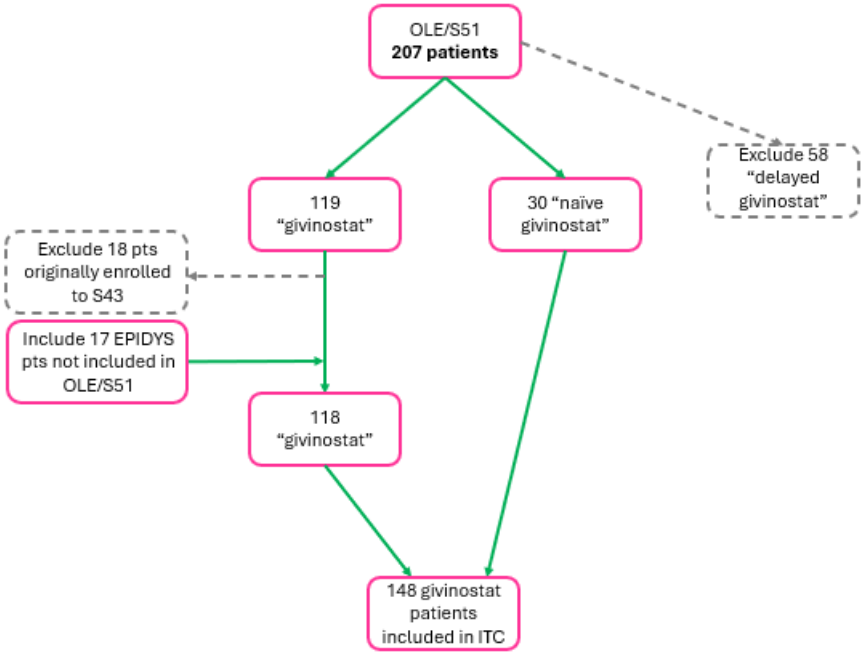
**Response:** The baseline data and results presented in the CSR for the OLE study (Study 51) are not identical to those for the ITC because the groups of included patients differ.

In the OLE study, 207 patients were enrolled;[a] however for the ITC, only 131 patients from the OLE study were included, plus an additional 17 patients from EPIDYS who

[a]All 207 patients took ≥1 dose of treatment and had ≥1 post-baseline efficacy measurement

were not enrolled in the OLE study. The flow of patients for the ITC is illustrated in Figure 3.

**Figure 3: Patients receiving givinostat who were included in the ITC**




Abbreviations: ITC, indirect treatment comparison; OLE, open-label extension; S43, Study 43; S51, Study 51.

We note that there were some minor errors with the text describing Table 23 (Document B) of the CS, as well as in the table itself, which may have caused confusion. The text should read "**101** patients [corrected from 102 patients] were enrolled in both EPIDYS and the OLE study; **17** patients [corrected from 16 patients] were enrolled in EPIDYS *and did not continue into the OLE study, whilst* 30 patients were receiving givinostat for the first time in the OLE study". A version of Table 23 with minor corrections is presented below.

**Table 23: Study design of the studies included in the indirect treatment comparison (corrected)**

| Study | Treatment intervention | N | Phase/ blinding | Centre | Study design | Sample size for ITC |
|---|---|---|---|---|---|---|
| EPIDYS (Study 48) (NCT02851797) | Givinostat | 118 | Phase 3, double-blind | Multicentre | RCT | 118 pts:<br>• 101 pts receiving givinostat subsequently enrolled to OLE<br>• 1 pt receiving givinostat failed screening for OLE‡<br>• 16 pts did not enrol in OLE‡ |
| | Placebo | 61 | | | | NA |
| OLE study (Study 51)† (NCT03373968) | Givinostat | 119 | Long-term study, open-label | Multicentre | Enrolling patients who have been previously treated in previous givinostat studies or who met all inclusion/ exclusion criteria for EPIDYS, but had baseline MRS VLFF in range ≤5% or >30% | 131 pts:<br>• 101 pts previously treated with givinostat in EPIDYS<br>• 30 pts who were givinostat naïve at study start¶ |
| | Delayed givinostat | 58 | | | | |
| | Naïve givinostat‡ | 30 | | | | |
| UK real-world data | CS stopped prior to transition to adult services | 43 | NA | London, Newcastle and Oxford | Retrospective case note review | 156 pts receiving ECM |
| | CS continued to adulthood | 113 | | | | |
| | CS naïve | 53 | | | | NA |

†Dec 2023 DCO; ‡Patients who received givinostat in EPIDYS and were included in the ITC but not enrolled in the OLE study (Study 51); ¶Met all the inclusion criteria and none of the exclusion criteria for EPIDYS, and not randomised as enrolment in the "off-target" group was completed, subjects received givinostat for the first time in the OLE study.
Abbreviations: CS, corticosteroid; DCO, data cut off; ECM, established clinical management; ITC, indirect treatment comparison; MRS VLFF, magnetic resonance spectroscopy vastus lateralis fat fraction; NA, not applicable, NR, not reported; OLE, open-label extension; pts, patients; UK, United Kingdom.

Baseline data for the 148 patients included in the ITC are provided in Table 24 of the CS and reproduced in Table 5.

**Table 5: Baseline characteristics of studies included in the indirect treatment comparison**

| | EPIDYS | OLE study | Pooled EPIDYS/ OLE study | UK real-world data | | Pooled ECM UK real-world data |
|---|---|---|---|---|---|---|
| **Treatment** | Givinostat | Givinostat | Givinostat | CS stopped | CS continued | Combined CS (=ECM) |
| **N** | 118 | 30 | 148 | 43 | 113 | 156 |
| **Age (years)** | | | | | | |
| **Mean (SD)** | 9.78 (2.02) | 10.5 (2.25) | 9.92 | NR | NR | NR |
| **Range** | 6.30 to 15.9 | 6.10 to 14.4 | 6.10 to 15.9 | NR | NR | NR |
| **CS start age (years)** | | | | | | |
| **Mean (SD)** | 6.11 (1.74) | 6.03 (2.37) | 6.09 (1.88) | 7.19 (1.73) | 7.20 (1.96) | 7.20 (1.90) |
| **Range** | 3.12 to 12.6 | 1.38 to 10.9 | 1.38 to 12.6 | 4 to 11.5 | 4 to 12.42 | 4 to 12.42 |
| **Race, n (%)** | | | | | | |
| **White** | 106 (89.8) | 22 (73.3) | 128 (86.5) | NR | NR | NR |
| **Asian** | 4 (3.4) | 2 (6.7) | 6 (4.1) | NR | NR | NR |
| **Black/ African American** | 3 (2.5) | 1 (3.3) | 4 (2.7) | NR | NR | NR |
| **Other** | 5 (4.2) | 5 (16.7) | 10 (6.8) | NR | NR | NR |
| **BMI (kg/m$^2$)** | | | | | | |
| **Mean (SD)** | 19.7 (4.10) | 20.2 (4.04) | 19.8 (4.08) | NR | NR | NR |
| **Range** | 12.4 to 30.6 | 13.9 to 30.5 | 12.4 to 30.6 | NR | NR | NR |
| **Time since first CS initiation (years)** | | | | | | |
| **Mean (SD)** | 3.62 (2.09) | 4.47 (2.65) | 3.80 (2.23) | NR | NR | NR |
| **Range** | 0.43 to 8.88 | 0.91 to 12.6 | 0.43 to 12.6 | NR | NR | NR |
| **Use of CS at baseline, n (%)** | | | | | | |
| **Deflazacort** | 91 (77.1) | 27 (90.0) | 118 (79.7) | NR | NR | NR |
| **Other steroid** | 27 (22.9) | 3 (10.0) | 30 (20.3) | NR | NR | NR |
| **Time to rise from floor (sec)** | | | | | | |
| **Mean (SD)** | 6.89 (7.43) | 5.57 (2.06) | 6.62 (6.71) | NR | NR | NR |
| **Range** | 2.60 to 60.2 | 3.00 to 9.50 | 2.60 to 60.2 | NR | NR | NR |
| **Time to 4SC (sec)** | | | | | | |
| **Mean (SD)** | 3.58 (1.25) | 3.58 (1.28) | 3.58 (1.25) | NR | NR | NR |
| **Range** | 1.80 to 7.10 | 1.80 to 6.60 | 1.80 to 7.10 | NR | NR | NR |
| **Time to walk/run 10 metres** | | | | | | |
| **Mean (SD)** | 5.56 (1.34) | 19.0 (74.6) | 8.28 (33.6) | NR | NR | NR |
| **Range** | 3.50 to 9.50 | 3.20 to 414 | 3.20 to 414 | NR | NR | NR |

Abbreviations: 4SC, 4-stair climb; BMI, body mass index; CS, corticosteroids; ECM, established clinical management; NR, not reported; OLE, open-label extension; SD, standard deviation; sec, second.

Unadjusted outcome results for the 148 patients are included in each of Table 28, 29 and 30 of the original submission. However, only age at loss of ambulation (LOA) results are based on observed data, and these results are summarised in Table 6.

**Table 6: Summary of age at LOA for 148 patients included in the ITC**

| Treatment (study) | N | Events | Median (95% CI) |
|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148 | 43 | 17.97 (15.40, NE) |

Abbreviations: CI, confidence interval; ITC, indirect treatment comparison; LOA, loss of ambulation; OLE, open-label extension.

**A15.** Were sensitivity analyses using different acceleration factors for the ITC carried out for age at LOV vs. age at NIV, and for age at LOV vs. age at FVC <1L? Could the results for these please be provided.

**Response:** Additional sensitivity analyses have been conducted for the matching-adjusted indirect treatment comparison (MAIC) between givinostat and ECM (based on the UK real-world data), with the acceleration factors estimated from the CINRG DNHS study applied. Table 7 presents a summary of the conducted analyses including details on the acceleration factors applied within the analyses.

**Table 7: Matching-adjusted indirect treatment comparisons conducted**

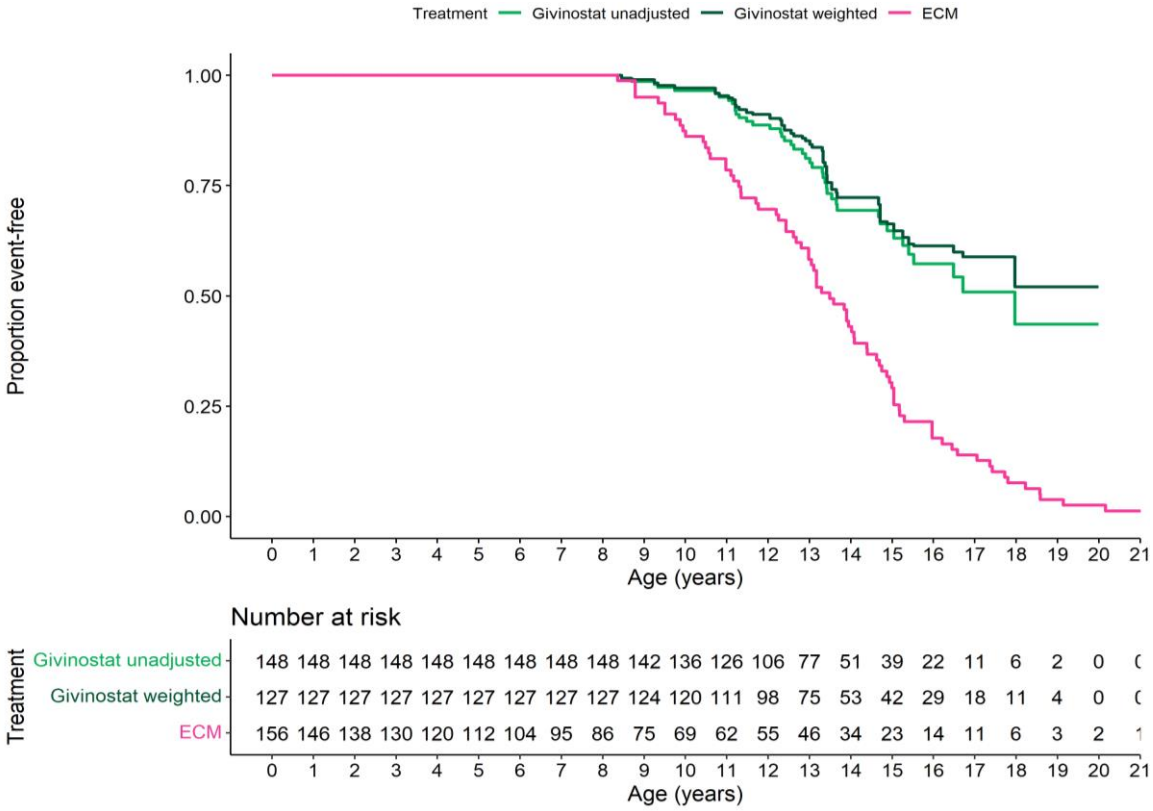
| Endpoint | Givinostat data | ECM data | Matching variables |
|---|---|---|---|
| **EPIDYS and OLE study vs. UK real-world data (base case analyses)** | | | |
| Age at LOA | Age at LOA KM | UK real-world data: Age at NIV KM with AF 0.73† | CS start age (years) |
| Age at NIV | Age at LOA KM with AF 1.37†‡ | UK real-world data: Age at NIV KM | |
| Age at FVC <1L | Age at LOA KM with AF 1.91¶ | UK real-world data: Age at FVC <1L KM | |

†AF estimated from CINRG age at LOA median and CINRG age at pFVC <50% median; ‡AF corrected from Appendix Table 17 in CS appendices; AF estimated from CINRG age at LOA median and CINRG age at FVC <1L median.
Abbreviations: 1L, 1 litre; AF, acceleration factor; CS, corticosteroids; ECM, established clinical management; FVC, forced vital capacity; KM, Kaplan-Meier; LOA, loss of ambulation; NIV, non-invasive ventilation; OLE, open-label extension; pFVC, predicted forced vital capacity.

## Age at loss of ambulation (sensitivity analysis)

The KM plots for age at LOA for givinostat patients for both unadjusted and weighted patient data, compared with patients receiving ECM (estimated using an acceleration factor) are presented in Figure 4.

**Figure 4: Kaplan-Meier plot for age at LOA MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**




Abbreviations: ECM, established clinical management; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; OLE, open-label extension; UK, United Kingdom.

Median age at LOA for givinostat treated patients was 18.0 years pre-weighting and not reached post-weighting, compared with 13.5 years for ECM treated patients (

Table 8). Patients treated with givinostat were significantly older at LOA compared with patients treated with ECM, with HR (95% CI) of 0.28 (0.18, 0.43) from the weighted comparison with robust SE; these results were aligned with results from the bootstrap estimation (HR [95% CI] 0.27 [0.19, 0.40];

Table 8).

**Table 8: Summary of age at LOA MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**

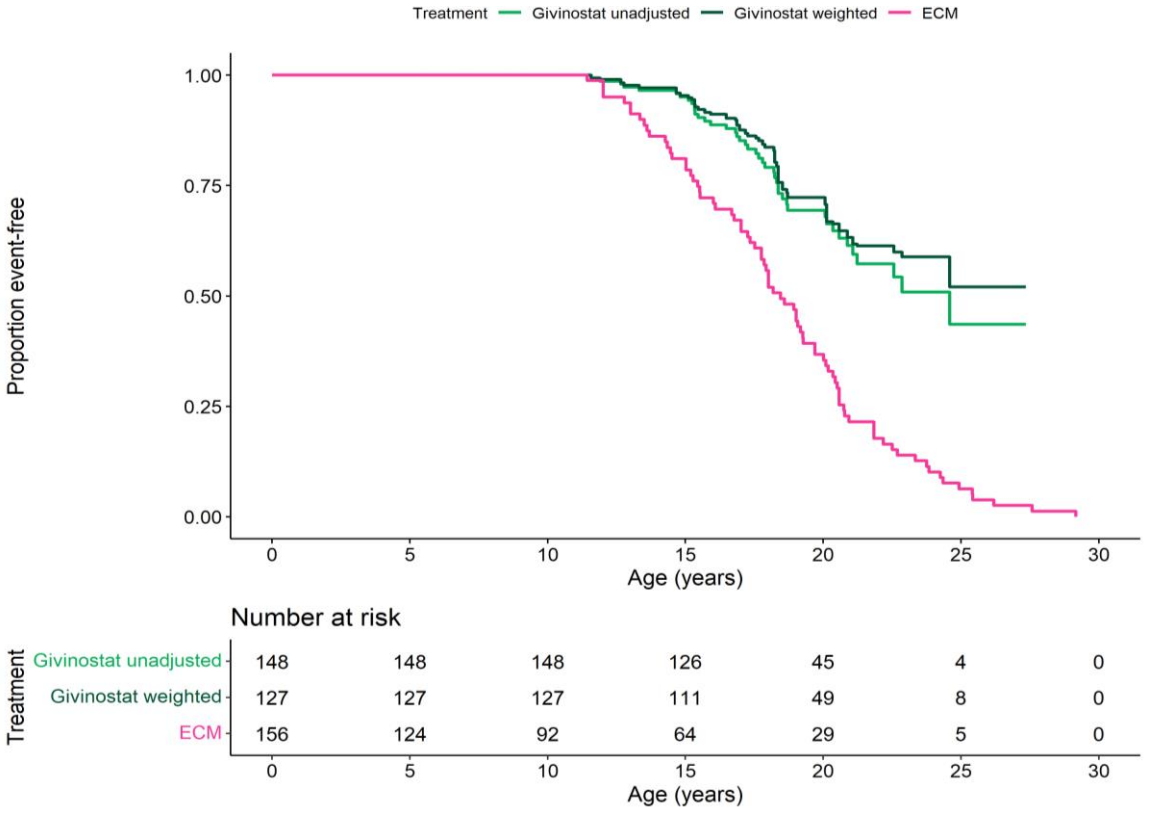
| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 17.97 (15.40, NE) | **0.338 (0.232, 0.492)** |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NE (15.52, NE) | Robust SE: **0.275 (0.176, 0.430)** Bootstrap: **0.274 (0.186, 0.400)** |
| ECM (UK real-world data) | 156.0 | 79 | 13.49 (12.98, 14.40) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error; UK, United Kingdom.

## Age at non-invasive ventilation (sensitivity analysis)

As noted in the CS, there were zero events for age at non-invasive ventilation (NIV) amongst the patients receiving givinostat during the study follow-up (see Figure 28 of the CS). However, applying the estimated acceleration factor of 1.37 (Table 7) to the data for age at loss of ambulation, KM curves for estimated age at NIV for givinostat patients for the unadjusted and weighted patient data, compared with patients receiving ECM are presented in Figure 5.

**Figure 5: Kaplan-Meier plot for age at NIV MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**




Abbreviations: ECM, established clinical management; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; OLE, open-label extension; UK, United Kingdom.

Median age at NIV for givinostat treated patients was 24.6 years pre-weighting and not reached post-weighting, compared with 18.5 years for ECM treated patients (

Table 9). Patients treated with givinostat were significantly older when receiving NIV, compared with patients treated with ECM with a HR (95% CI) of 0.28 (0.18, 0.43) from the weighted comparison with robust SE; these results were aligned with the results of the bootstrap estimation (HR [95% CI] 0.27 [0.19, 0.40];

Table 9).

**Table 9: Summary of age at NIV MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**

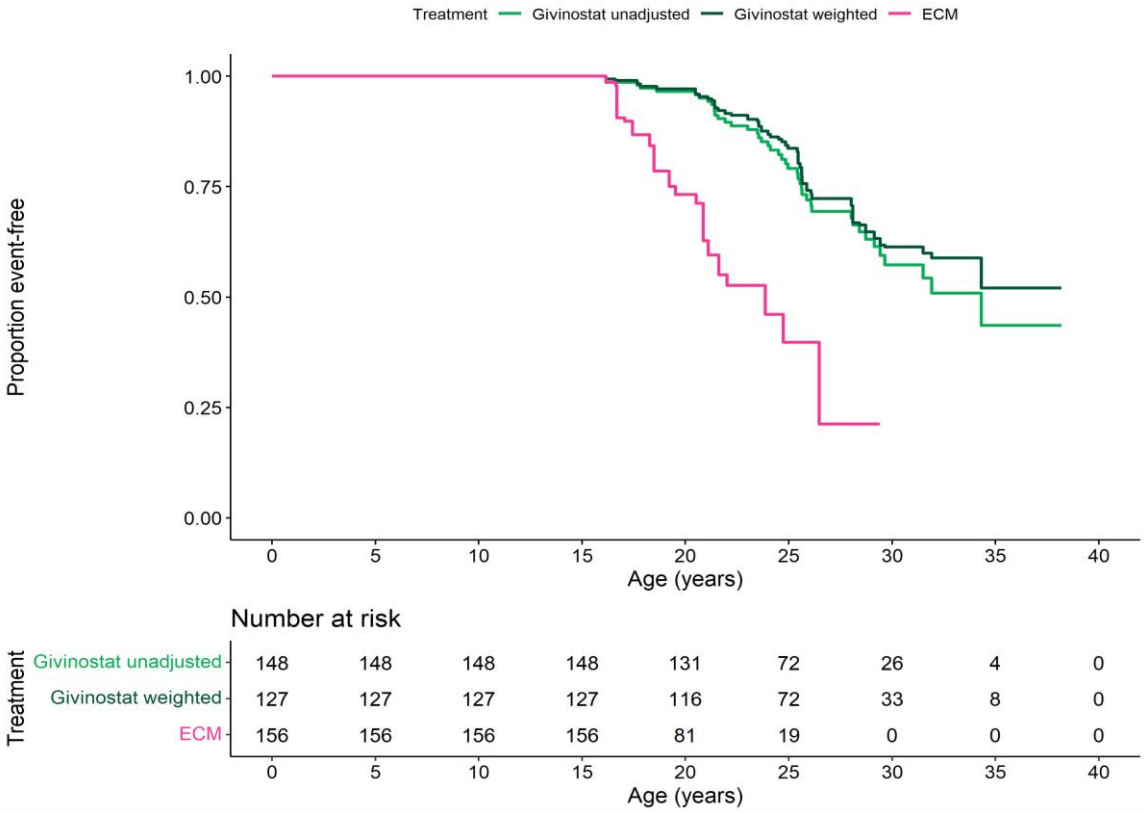
| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 24.59 (21.07, NE) | **0.338 (0.232, 0.492)** |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NE (21.23, NE) | Robust SE: **0.275 (0.176, 0.430)** Bootstrap: **0.274 (0.186, 0.400)** |
| ECM (UK real-world data) | 156.0 | 79 | 18.46 (17.76, 19.70) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; NIV, non-invasive ventilation; OLE, open-label extension; SE, standard error; UK, United Kingdom.

## Age at forced vital capacity < 1L (sensitivity analysis)

As with age at NIV, there were zero events for forced vital capacity (FVC) <1L amongst the patients receiving givinostat during the study follow-up. However, applying the estimated acceleration factor of 1.91 (Table 7) to the age at LOA data, KM curves for estimated age at FVC <1L for givinostat patients for the unadjusted and weighted patient data, compared with patients receiving ECM are presented in Figure 6.

**Figure 6: Kaplan-Meier plot for age at FVC <1L MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**




Abbreviations: 1L, 1 litre; ECM, established clinical management; FVC, forced vital capacity; MAIC, matching-adjusted indirect comparison; OLE, open-label extension; UK, United Kingdom.

Median age at FVC <1L for givinostat treated patients was 34.3 years pre-weighting and not reached post-weighting, compared with 23.9 years for ECM treated patients (Table 10). Patients treated with givinostat were significantly older when reaching FVC <1L compared with patients treated with ECM with a HR (95% CI) of 0.23 (0.15, 0.35) from the weighted comparison with robust SE; these results were aligned with the results of the bootstrap estimation (HR [95% CI] 0.23 [0.16, 0.31]; Table 10).

**Table 10: Summary of age at FVC <1L MAIC: givinostat (EPIDYS and OLE study) vs. ECM (UK real-world data)**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 34.32 (29.41, NE) | **0.254 (0.168, 0.382)** |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NE (29.64, NE) | Robust SE: **0.229 (0.150, 0.352)** Bootstrap: **0.231 (0.162, 0.308)** |
| ECM (UK real-world data) | 156.0 | 67 | 23.86 (21.62, 26.47) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: 1L, 1 litre; CI, confidence interval; ECM, established clinical management; ESS, effective sample size; FVC, forced vital capacity; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error; UK, United Kingdom.

## Summary of sensitivity analysis results

The results of the sensitivity analyses which apply the acceleration factors derived from the CINRG study to the MAIC comparing givinostat with ECM (based on the UK real-world data), display comparable results to results presented in the CS and Appendix document. For each of the three outcomes (age at LOA, age at NIV, age at FVC <1L), the results suggest that the boys treated with givinostat have a significantly reduced hazard of experiencing an event compared with ECM.

**A16.** For Section B.3.3.1, is the unpublished UK-real world data suggesting that, in clinical practice, patients may lose their ambulation earlier with a median age at loss of ambulation of 12.1 years reference 178 Pietrusz?

**Response:** In Section B.3.3.1 in the CS, the advantages and limitations of the published natural history model (NHM) are discussed.[22] The key limitation is, due to sparse data, the exponential distribution was used to fit the multi-state model. Its use has resulted in clinically implausible mean durations in health states (8a) and (8b) – as recognised and discussed in the published paper. Additionally, as discussed in the vamorolone NICE submission and highlighted by comparisons with external data, the median age at loss of ambulation estimated by the NHM appears to be over-estimated.[23–25]

The CS explored the potential for over-estimated transition probabilities in the published NHM, based on estimates that the median age of LOA is 15.5 years. Both the unpublished UK real-world data and the subgroup of patients included in the MAIC sensitivity analyses (CINRG DNHS) suggest that, in clinical practice, patients may lose ambulation earlier than that reported in the NHM, with a median age at LOA of 12.1 years and 13.0 years, respectively.

As described in Section B.3.3.1, two approaches have been explored to align long-term outcomes from the published NHM with external UK data sources. Updated NHM (analysis 2) is used in the base case; this adjustment aligns the NHM with a median age at LOA of 12.1 and the proportion surviving at 50-years of 2.8%. The NHM

(analysis 2) is demonstrated to align with external data and expectations in UK clinical practice.

**A17.** Section B.2.8.1 Table 25: Why was the feasibility of MAIC on the primary effectiveness outcome in EPIDYS (mean change in the time taken to complete a standard four-stair climb between baseline and 18 months) not assessed?

**Response**: Although mean change in time to complete a four-stair climb is a validated outcome measure used extensively in clinical trials, it is rarely assessed in clinical practice. This is supported by its exclusion from the Project HERCULES CEM which was developed using previously identified health states in the published literature; input from clinicians, academics, patients, and caregivers; and reflects outcomes commonly collected in clinical trials and real-world practice. Therefore, this was not an outcome of interest for the CEM and consequently not a key priority for the MAIC analyses.

In addition, this outcome was not reported for the UK real-world data, nor for the relevant set of ECM patients from CINRG DNHS who were included in the MAIC sensitivity analysis. For the latter, limited four-stair climb outcome data were available from an earlier published analysis, however this was only for a CINRG DNHS sample size of 181 patients,[26] compared with 261 patients used in the sensitivity analyses of the CS.[25] In addition, the number of patients reporting age at time to climb four stairs ≥5 seconds and ≥10 seconds was much smaller, at 47 patients and 85 patients, respectively. Finally, there were no available baseline characteristics for these subgroups upon which matching could be conducted.

**A18. <u>Priority question:</u> The North Star database includes data on additional functional covariates that the company say were not available for use in the MAIC (Table 24, CS Doc B). Please can the company provide further explanation as to why they were not able to match on additional covariates, such as NSAA score, time to rise from floor and VL MFF. (See Zambon et al [2022] DOI: 10.1111/dmcn.15176).**

**Response:** These datasets were not identical and therefore baseline characteristic could not be interchanged.

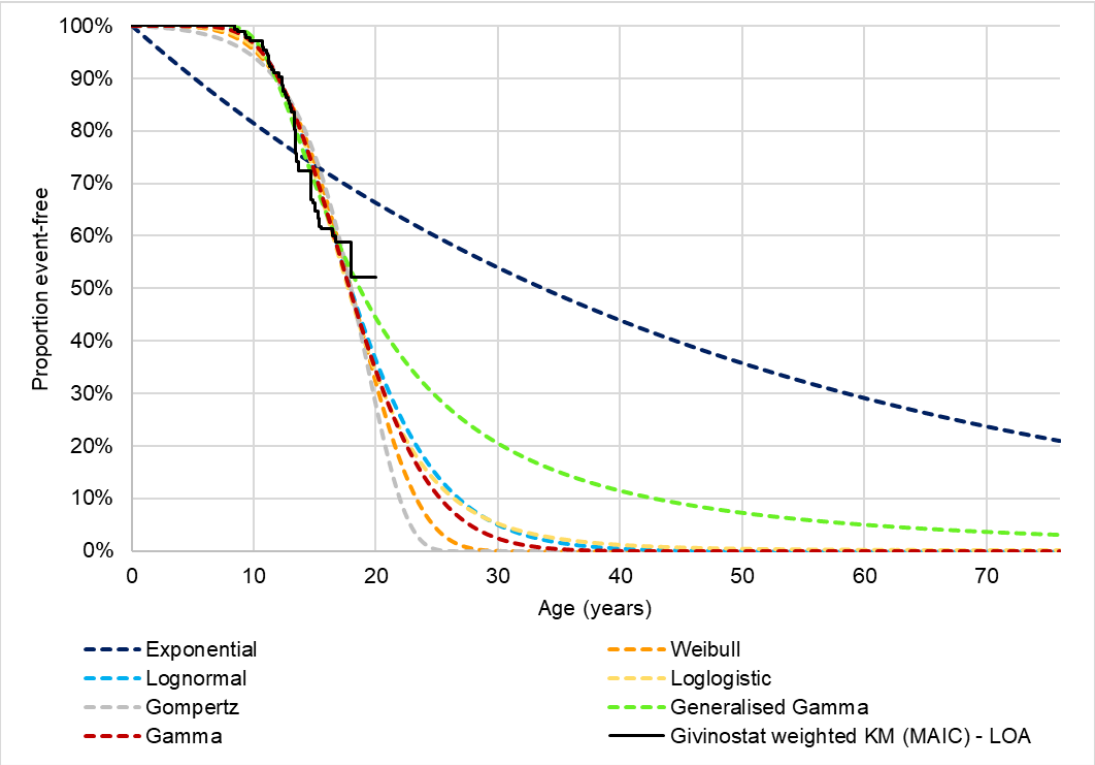
In the Zambon 2022 publication, 293 patients were included in the dataset and were analysed for LOA and the impact of baseline characteristics on this outcome. No non-ambulatory milestones were considered.[27] In contrast, in the UK real-world data set included in the MAIC, 156 patients were suitable for inclusion in the MAIC analyses and both LOA, and pulmonary outcomes, were available for these patients. This ensured consistency of reporting across disease progression milestones, excluding the potential for any contradictory results to be presented. In addition, the data available from the Pietrusz analysis included the most recent follow-up dates, as some included data were collected after the Zambon analyses were completed. Therefore, the Pietrusz UK real-world was the most relevant for the CS, but without access to the individual patient-level data, it was not possible to include additional baseline characteristics in the matching process for the MAIC.

# Section B: Clarification on cost-effectiveness data

**B1.** Why does the exponential model in Figures 41-43 appear to start from 90% instead of 100%? If the model is fit from age 0 then this earlier part should be included in the figures.

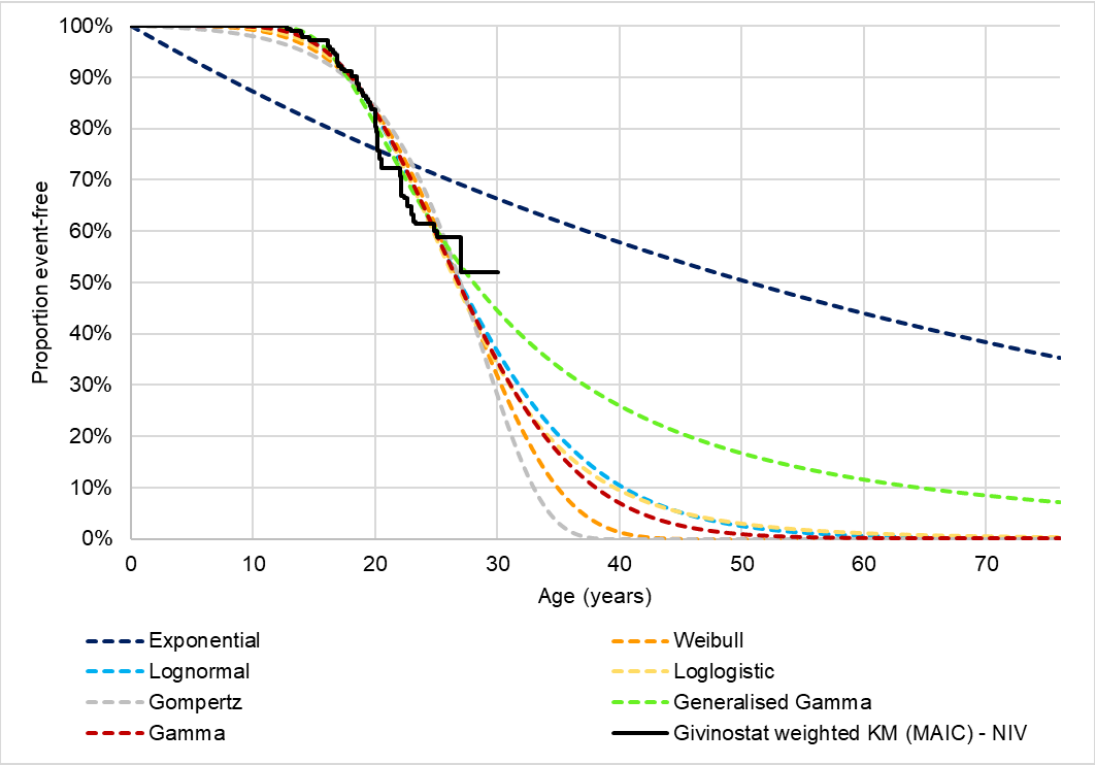
**Response:** The parametric models were fit to the MAIC-weighted Kaplan-Meier data starting from age 0. In the original CS, Figures 41–43 depicted the extrapolated curves across the model time horizon, starting from age 6 and spanning a 70-year horizon. However, in response to the EAG's question, we have updated these figures below to show the extrapolations from a starting age of 0.

**Figure 7: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at loss of ambulation (update of Figure 41 from original CS)**



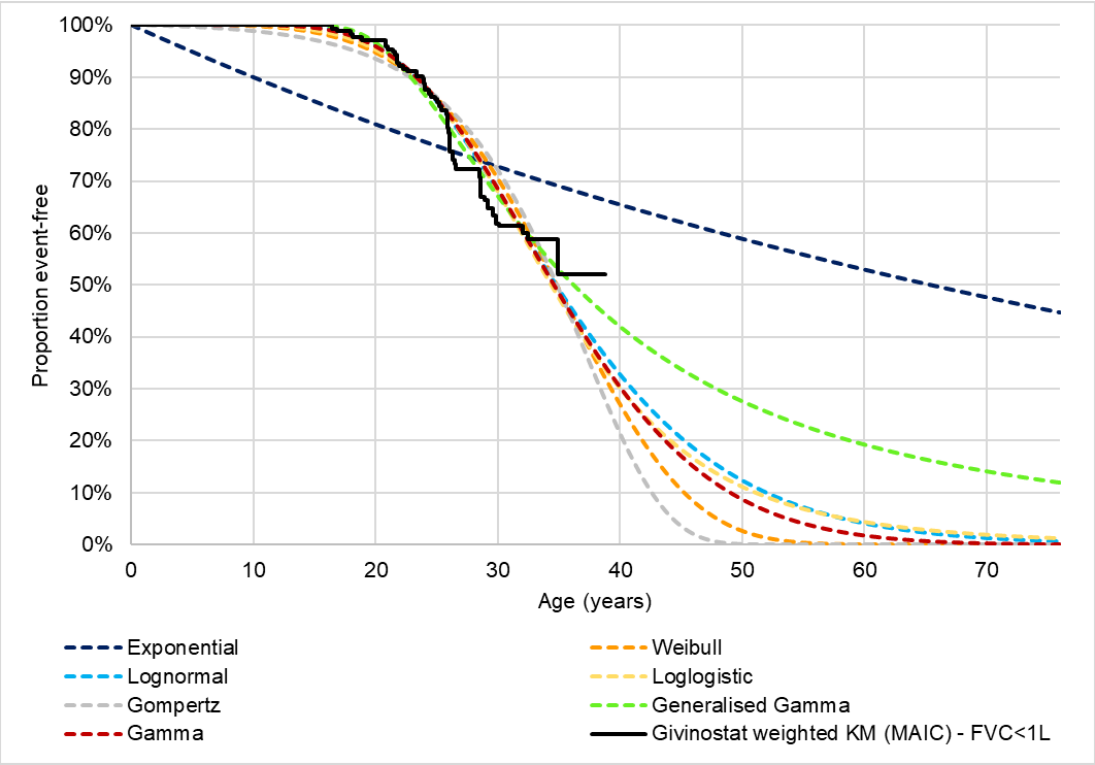

Abbreviations: CS, Company submission; KM, Kaplan-Meier; LOA, loss of ambulation; MAIC, matched adjusted indirect comparison.

**Figure 8: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at non-invasive ventilation (update of Figure 42 from original CS)**




Abbreviations: CS, Company submission; KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison; NIV, non-invasive ventilation.

**Figure 9: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at FVC<1L (update of Figure 43 from original CS)**




Abbreviations: CS, Company submission; FVC, forced vital capacity; KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison.

**B2.** In Section B.3.3.2 it is stated that the AIC and BIC rankings for loss of ambulation, non-invasive ventilation, and FVC<1L are the same due to the MAIC and that this is explained in Section B.2.8.4. It is not clear from this earlier section. Please provide clarification as to the reason the rankings are the same**.**

**Response:** The AIC and BIC rankings for loss of ambulation, non-invasive ventilation, and FVC<1L are the same due to the assumptions underpinning the MAIC-weighted Kaplan-Meier data. We apologise for the oversight in the original CS. The correct reference should have stated that these assumptions are described in the original CS in *Section B.2.8.2* (i.e., "Overview of the methodology" of the ITCs) and in Table 26 in *Section B.2.8.3* (i.e., "ITC analyses conducted"). The information from these sections is summarised below, with additional detail provided.

As shown in Table 26 in the original CS, the non-invasive ventilation and FVC<1L endpoints are estimated based on the loss of ambulation KM data and acceleration factors accounting for the ratio of median age at loss of ambulation and median age of non-invasive ventilation, and median age at loss of ambulation and median age of FVC<1L, respectively.

Applying an acceleration factor assumes that the underlying shape of the survival curve (e.g., derived from a Kaplan-Meier estimate or a parametric model) is consistent across endpoints. The only difference between the endpoints is the time scale at which events occur. Acceleration factors effectively scale the time axis without altering the inherent fit of the survival function to the data.

As a result, the likelihood values for different outcomes are scaled by a fixed value which consequently adds a fixed value to the log-likelihood. Given that the number of parameters estimated and the sample size are consistent across the endpoints, the relative ranking of the AIC and BIC remains the same across endpoints – as shown in Table 49 in the original CS.

**B3.** In Section B.3.8 the company explains that no treatment effect is assumed beyond loss of ambulation. This is directly contradicted by the hazard ratios in Table 51, which indicate that givinostat is modelled to have a strong impact on transitions beyond the loss of ambulation (i.e., transitions to state 4 and above). Please can you confirm that givinostat is assumed to have an effect beyond loss of ambulation and clarify what was meant in Section B.3.8?

**Response:** As detailed in Section B.3.8 and B.3.3.4 in the CS, no direct treatment effect is assumed beyond loss of ambulation for givinostat. The hazard ratios for transitions into health states 5–8 presented in Table 51 in the original CS (aligning with the age at non-invasive ventilation and age at FVC<1L endpoints) reflect the effect of delaying the age at loss of ambulation event achieved with givinostat relative to ECM. These hazard ratios for endpoints occurring after loss of ambulation compare the likelihood of an event between two groups defined by the age at loss of ambulation (not by treatment) and do not account for direct treatment effects of givinostat relative to ECM. We understand that this is a complex matter, and further details are provided below.

In Section B.2.8.2 (i.e., "Overview of the methodology" of the ITCs) and Section B.2.8.3 (i.e., "ITC analyses conducted") of the original CS, the methodology for estimating Kaplan-Meier data related to the ECM treatment and age at non-invasive ventilation and age at FVC<1L outcomes is explained. This methodology involves calculating acceleration factors, which are applied to Kaplan-Meier data to generate the predicted outcomes for these endpoints under ECM.

Since no direct data are available for givinostat regarding the age at non-invasive ventilation and age at FVC<1L outcomes, the same acceleration factors used for ECM are applied to the age at loss of ambulation Kaplan-Meier data for givinostat to estimate the outcomes for the later endpoints in the givinostat arm. For example, the unadjusted Kaplan-Meier data for givinostat indicates a median age of 17.97 for the occurrence of loss of ambulation (Table 28 in the original CS). This value is then multiplied by acceleration factors of 1.5 to estimate age at non-invasive ventilation (resulting in a median age of 27.00, Table 29 in the original CS) and 1.94 to estimate age at FVC<1L (resulting in a median age of 34.90, Table 30 in the original CS). As described, the outcomes for age at non-invasive ventilation and age at FVC<1L are purely driven by the age at loss of ambulation and do not account for the ongoing potential treatment effect with givinostat. These estimates serve as the basis for the MAIC analyses, from which the hazard ratios are derived.

In other words, if the median age for loss of ambulation with givinostat was 12.28—matching that of the ECM arm—this method implies that the median age for requiring non-invasive ventilation and reaching FVC < 1L would also align with the ECM arm. Consequently, the hazard ratios for transitions into health states 5 through 8 would equal one.

As mentioned in Section B.2.8.2, this methodology assumes that the relationship between age at loss of ambulation and the age at non-invasive ventilation and age at FVC<1L outcomes is consistent for both the givinostat and ECM treatment arms. This is supported by the literature. As described in Section B.2.8.2 and Section 3.3.4 of the original CS, Humbertclaude et al. 2012 found that age at loss of ambulation is predictive of both the age at which the peak FVC is realised, and the absolute peak obtained FVC.[28] These findings are supported by McDonald et al. 2018b who demonstrate age at loss of ambulation predicts time to an absolute FVC of 1L and Levine et al. 2023 who show that the decline in percentile predicted FVC and total lung capacity correlate with age and loss of ambulation.[29,30] Therefore, it is expected that the improved skeletal muscle integrity/ function achieved through treatment with givinostat compared to ECM, as demonstrated through the earlier outcomes observed in EPIDYS and the OLE study, will translate to improved longer term outcomes – regardless of whether a patient remains on treatment with givinostat.

There may be additional treatment effects associated with givinostat beyond age at loss of ambulation. However, these are not captured by the cost-effectiveness model (CEM). The published data describe the relationship between earlier outcomes and longer-term outcomes for patients receiving ECM. Assuming the same relationship holds for givinostat as for ECM is conservative for two reasons:

- Firstly, improving the skeletal muscle integrity/function and delaying the loss of ambulation, as observed with givinostat in EPIDYS and the OLE study, may have an exaggerated impact on longer-term outcomes.
- Secondly, continued treatment with givinostat may lead to a treatment effect above and beyond what we would expect to see translating from delaying the loss of ambulation.

Nevertheless, the treatment effect of givinostat on these longer-term outcomes is unknown. Therefore, the CEM assumes that the relationships between age at loss of ambulation and the longer-term outcomes are the same for givinostat as those observed for ECM. This means that no treatment effect is assumed beyond age at loss of ambulation i.e., it is expected that the delay in loss of ambulation will translate to improved outcomes regardless of the ongoing givinostat treatment.

**B4. <u>Priority question:</u> Please provide a stronger justification for assuming that the givinostat effect continues even after treatment has been discontinued. Please implement a scenario in the CEM that assumes the effect is removed after discontinuation (i.e., transition probabilities revert to those on ECM).**

**Response:** As outlined in the response to Clarification Question B3 and Section B.3.3.4 of the original CS, no direct treatment effect for givinostat is assumed beyond the loss of ambulation milestone. Therefore, any assumptions regarding the treatment effect continuing after discontinuation pertain only to this endpoint.

In EPIDYS, seven patients discontinued givinostat (5.9%) due to consent withdrawn (n=4, 3.4%) and AEs (n=3, 2.5%) across the 18 month follow-up.[1] None of these patients had reached the loss of ambulation milestone. In the OLE study, 21 patients discontinued givinostat (10.1%) due to AEs (8, 3.9%), consent withdrawn (n=7, 3.4%), other reasons (n=4, 1.9%), and lost to follow-up (n=2, 1.0%) across the 39.6 month

(1,204.2 days) follow-up.[11] Twelve of these patients discontinued prior to the loss of ambulation milestone.

The treatment effect on the age at loss of ambulation is derived from the entire study population, which includes both patients who continued treatment and those who discontinued. As a result, the observed treatment effect reflects an average that accounts for any diminished or loss of effect in those who discontinued. Introducing a scenario where the treatment effect is removed entirely after discontinuation would artificially exaggerate the negative impact of discontinuation, which is already incorporated into the observed data. This would lead to biased outcomes. For these reasons, this analysis has not been conducted.

Additionally, givinostat may have lasting effects after discontinuation, depending on the duration and stage at which treatment was stopped. Given the small number of patients who discontinued givinostat before reaching the loss of ambulation milestone, any such scenario would likely have minimal impact on the results.

**B5. <u>Priority question:</u> Can you please provide us with the Economic Model revealing the calculations for Hazard Ratios using the SOLVER functionality in Microsoft Excel. This could be facilitated with the use of a button linked to a VBA macro for each use of SOLVER. The macro would set all options to necessary settings and then run SOLVER. The usual Reset to defaults button should be updated to be able to restore the model after running the Solver macro. Please note the reset to defaults button "This page only" option doesn't reset all options. For example, it doesn't reset "Perspective" or inclusion of caregiver utilities on the "Settings" tab and should be updated accordingly. The HRs were noted in the CS to use the SOLVER functionality are:**

i. **NHM [analysis 1] transitions from health states 8a to 8b on P.147 of CS.**

ii. **NHM [analysis 2] transitions from health states (1) to (2), (2) to (3), (3) to (4), and (8a) and (8b) on P.148 of CS .**

iii. **CEM comparative efficacy of Givinostat transitions from health states (1) to (2), (2) to (3), and (3) to (4), such that the predicted median age at loss**

**of ambulation from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat loss of ambulation data on P.152 of CS.**

iv. **CEM comparative efficacy of Givinostat transitions from health states (4) to (5), (4) to (6), and (5) to (7a), such that the predicted median age at ventilation from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat non-invasive ventilation data on P.152 of CS.**

v. **CEM comparative efficacy of Givinostat transitions from health states (6) to (7b), (7a) to (8a), and (7b) to (8b), such that the predicted median age at FVC<30% from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat FVC<1L data on P.153 of CS.**

**Response:** Thank you for your suggestions. We acknowledge that the recommendations you have made would enhance the transparency and user-friendliness of the CEM. As such, we have addressed each of them in the updated CEM titled "Givinostat CEM in DMD_NICE_PAS_CQ [CON]." The changes made are described below.

The issue with the reset to defaults button “This page only” option not resetting all selections was due to the drop-down list selections being routed through the “Cell links” sheet. This has been updated so that all drop-down list selections are now routed through the same sheet where the drop-down list is presented to the user. This update ensures that reset to defaults button “This page only” option resets all selections on the relevant sheet. Note: the option to include or exclude caregiver utilities was previously available on both the “Settings” sheet and the “HRQoL data” sheet. To ensure proper functionality of the reset feature, this option has been removed from the “Settings” sheet and is now only available on the “HRQoL data” sheet.

The SOLVER functionality has been incorporated into the VBA code and can be executed using the buttons on the “Natural history” and “Clinical data” sheets. On the

“Natural history” sheet, users must select the analysis type (i.e., NHM [analysis 1] or NHM [analysis 2]) before running the SOLVER calculations:

- In NHM (analysis 1), only the hazard ratios for transitions from health states (8a–8b) to death are varied.

- In NHM (analysis 2), the hazard ratios for transitions from health states (1) to (2), (2) to (3), and (3) to (4) are varied first, followed by the hazard ratios for transitions from health states (8a–8b) to death.

On the “Clinical data” sheet, the hazard ratios applied in the givinostat arm relative to the ECM arm are varied across all health states:

- Health states (1) to (2), (2) to (3), and (3) to (4), such that the predicted median age at loss of ambulation from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat loss of ambulation data.

- Health states (4) to (5), (4) to (6), and (5) to (7a), such that the predicted median age at ventilation from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat non-invasive ventilation data.

- Health states (6) to (7b), (7a) to (8a), and (7b) to (8b), such that the predicted median age at FVC<30% from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat FVC<1L data.

This functionality was not included in the original CS due to the inherent complexity and associated caveats. Specifically:

- The CEM uses discrete one-month cycles rather than defining time as a continuous variable. This introduces inherent limitations where an exact solution cannot be derived from the SOLVER functionality, and multiple solutions may be found based on the optimisation.

- These complexities necessitate the use of the “Evolutionary” calculation approach in SOLVER, defined in the VBA code.

The original CS employed a simpler method that minimised the difference between rounded live results and rounded goal results (to one decimal place). The updated approach improves on this by using SOLVER to minimise the raw difference between live results and the goal, avoiding reliance on rounding. Although small fluctuations in the ICER may occur due to variations in hazard ratios beyond three decimal places, these fluctuations are negligible. The results remain robust and fit for decision-making purposes, with no material impact on the conclusions derived from the model.

We note that the EAG has requested that the VBA code reset all model parameters to the base case settings before running the SOLVER calculations. This functionality has been intentionally omitted to provide flexibility in running the SOLVER in a CEM that may not be configured based on base case values. However, users who wish to reset the CEM to base case values before running the SOLVER calculations can do so by using the “reset to base case” button, located at the top of each sheet. This allows users to ensure the model aligns with base case settings before initiating the SOLVER functionality.

**B6.** The transition probability calculations in "Natural history" and "Matrix algebra" appear to repeat a lot of what is completed in "Transitions2" and "Engine_2". Are these calculations in the former redundant or are they used by the model?

**Response:** We recognise that some calculations may appear repetitive; however, this approach was intentionally taken to prioritise transparency, improve user-friendliness, and avoid excessively lengthy and complex calculations that could impede effective quality checking. Each sheet in the model serves a specific and distinct purpose, as detailed below:

- **“Natural history” sheet:** This sheet provides the transition intensities based on the NHM published in Broomfield et al. 2024, along with the estimated transition probability matrices.[22] From row 125 onward, it calculates the patient flow for the ECM arm across the eight health states over the model’s time horizon. While the estimated transition probabilities and calculations from row 125 onward are not directly used in the model, they support the development of ECM predictions prior to adjustments for background mortality. Specifically, these outputs inform the SOLVER calculations required to determine the hazard ratios needed to align the NHM with expected ECM outcomes in UK clinical

practice. This alignment ensures the published NHM accurately reflects anticipated results with ECM.

- **“Matrix algebra” sheet:** This sheet calculates the cycle-adjusted transition intensities by multiplying the transition intensities from the “Natural history” sheet by the model’s cycle length. These adjusted intensities are used to estimate transition probabilities, which are then presented in the “Natural history” sheet. While these probabilities are not directly used in the model, they are used for developing ECM predictions before incorporating background mortality adjustments.
- **“Transitions2” sheet:** This sheet takes the transition intensities from the “Natural history” sheet, and multiplies them by the model’s cycle length, and estimates the corresponding transition probabilities per cycle. Background mortality caps are then applied to these probabilities. The adjusted transition probabilities generated in this sheet are directly used in the model engine (“Engine_2” sheet).
- **“Engine_2” sheet:** Using the transition probabilities from the “Transitions2” sheet (which include background mortality caps), this sheet calculates the distribution of patients across the eight health states. These distributions are used for estimating costs and QALYs within the model.

**B7.** Several important sheets are hidden and poorly documented. Please explain the general purpose of TMat1/2, how it is used in the calculation of Transitions1/2, and whether it has any impact on Engine1/2 or the final cost-effectiveness results.

**Response:** The calculations in the “TMat1” and “TMat2” sheets are remnants from the original Project HERCULES CEM. While they are used to inform columns AV and beyond in the “Transitions1” and “Transitions2” sheets, they do not contribute to any further calculations or outputs in this model.

As outlined in the response to clarification questions during the vamorolone NICE appraisal, the original Project HERCULES CEM included two approaches for estimating health state transitions: the “simple approach” and the “full approach”.[23] Consistent with the rationale provided in the vamorolone NICE submission, this model uses the simple approach, and the full approach has not been removed.

The simple approach assumes that patients can only transition to the next health state or to the death state in each cycle, meaning multiple transitions within a single cycle are not allowed. This assumption is supported by the model's one-month cycle length, which is sufficiently granular to allow for progression across one health state only in each cycle. The advantages of this simplified approach include reduced computational complexity and straightforward incorporation of background mortality and treatment effects into the transition probabilities.

In contrast, the full approach allowed for multiple transitions per cycle, enabling patients to skip health states. However, implementing and evaluating this method in Microsoft Excel® is challenging and significantly increases the complexity of the model. TMat1 and TMat2 are used to calculate the exponential of the matrix of transition intensities, using the eigen-decomposition. This provides the full set of transition probabilities for the model, accounting for the possibility of multiple transitions occurring in a single cycle. Further details on this approach to calculating the exponential can be found in Jones et al. 2017.[31]

The use of the simple approach has been accepted in the recently published vamorolone NICE submission, further reinforcing its validity and practicality for this model.

**B8. <u>Priority question:</u> Are Treatment administration and related monitoring costs for Givinostat expected to be the same as Standard of Care (SoC)? These costs were not captured in the CEM and our clinical advisors do expect treatment administration and monitoring to be different for Givinostat in comparison to SoC. Please provide an updated economic model capturing the costs related to the frequency and intensity of treatment administration and treatment monitoring expected to take place in tertiary setting or secondary setting for patients who live for away (in-patient or out-patient). These may also be related to cardiology, endocrine and bone health.**

**Response:** In the original CS, no administration costs were assumed for either givinostat or corticosteroids as both are oral therapies. This approach aligns with the assumptions accepted in previous NICE appraisals for ataluren and vamorolone (HST22, GID-TA11135).[8,23] Furthermore, ITF is collaborating with *"Polar Speed*" to implement a direct-to-home service for givinostat. Consequently, in UK clinical

practice, it is anticipated that givinostat will incur similar dispensing fees compared to corticosteroids, ataluren, or vamorolone.

We acknowledge the concerns raised by the EAG regarding clinician expectations for treatment administration and monitoring. While we maintain that givinostat itself does not incur administration costs, the SPC for givinostat recommends regular monitoring of platelet counts and triglycerides to inform potential dosage adjustments.[14] Specifically:

- **Blood counts** should be monitored every two weeks during the first two months of treatment, at month three, and every three months thereafter.
- **Triglyceride levels** should be monitored at one month, three months, six months, and then every six months thereafter.

Monitoring is important during the initial stages of treatment as patients work towards stabilising on an appropriate dose whilst managing the risk of thrombocytopaenia and hypertriglyceridaemia, which were observed in 33% and 23% of patients on the givinostat arm in EPIDYS. However, once the patient has reached a stable dose and the safety profile is manageable, the need for ongoing monitoring will fit into current patient review schedules. Therefore, it is anticipated that over time, monitoring will be reduced. This approach aligns with the observed reduction in adverse events after three months of treatment compared to the first three months of treatment – as presented in Section B.2.9.1 of the CS.[32]

To address the EAG's concerns, the costs of monitoring have been included in the updated CEM, titled “Givinostat CEM in DMD_NICE_PAS_CQ [CON].” The option to include these costs is in the “Cost data” sheet. The assumed frequencies of blood count and triglyceride tests align with the SPC recommendations and are presumed to occur in outpatient paediatric services, incurring a cost of £208 per outpatient appointment and £2 per test for integrated blood services (based on NHS Reference Costs 2023/24).[14,33] Table 11 details the resource use and costs applied to the givinostat arm in the CEM.

Including these monitoring costs increases the ICER from [redacted] to [redacted], representing a 0.8% increase (inclusive of the PAS) - Table 12. As noted, the need for

monitoring is expected to decrease over time. However, this reduction has not been accounted for in the updated CEM, ensuring a conservative estimate of the monitoring costs. Therefore, the scenario presented reflects the maximum anticipated impact of monitoring costs on the ICER.

**Table 11: Monitoring costs applied in the givinostat arm**

| | Blood counts | Triglycerides | Outpatient appointment |
|---|---|---|---|
| **Cost** | £2.00 | £2.00 | £208.00 |
| | **Frequency of resource use per month** | | **Cost per month** |
| **Month 1** | 2.00 | 1.00 | 2.00 | £422.00 |
| **Month 2** | 2.00 | 0.00 | 2.00 | £420.00 |
| **Month 3** | 1.00 | 1.00 | 1.00 | £212.00 |
| **Month 4** | 0.00 | 0.00 | 0.00 | £0.00 |
| **Month 5** | 0.00 | 0.00 | 0.00 | £0.00 |
| **Month 6+** | 0.33 | 0.17 | 0.33 | £70.33 |
| **Source** | NHS Reference Costs 2023/24; DAPS 999 Unknown; Integrated Blood Services. SPC.[14,33] | NHS Reference Costs 2023/24; DAPS 999 Unknown; Integrated Blood Services. SPC. | NHS Reference Costs 2023/24; Outpatient care, NCL 420 Paediatric Service. Non-admitted F2F attendance, follow-up. | |

Abbreviations: DAPS, Directly Accessed Pathology Service; F2F, face-to-face; NCL, non-consultant led; NHS, National Health Service; SPC, Summary of Product Characteristics.

**Table 12: Clarification Question 8 | Scenario analysis with givinostat monitoring costs (with PAS)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc costs (£) | Inc LYG | Inc QALYs* | ICER (£/ QALY)* |
|---|---|---|---|---|---|---|---|
| **Givinostat** | [redacted] | 21.9 | 19.3 | | | | |
| **ECM** | £99,448 | 14.6 | 6.1 | [redacted] | 7.3 | 22.4 | [redacted] |

*Including the 1.7 severity modifier.
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.

**B9. <u>Priority question:</u> Please include costs not captured by the Project HERCULES UK CPRD study (Morgan et al. 2024) such as tertiary care or medical aids in the economic model.**

**Response:** In Section B.3.5.1, Table 70 of the original CS, we highlighted that Morgan et al. 2024 provide cost data associated with primary care, prescriptions, outpatient appointments, A&E attendances, and inpatient admissions.[34] As described in the same section, this study represents the most robust source of cost and resource use identified for this analysis. These data reflect a large cohort (639 patients), are UK-specific, represent the most recent data, and align with the NICE reference case i.e. costs relate to NHS and PSS resources and are valued using the prices relevant to the NHS and PSS. Furthermore, the data show a clear and expected increase in costs as the disease progresses across health states, which is consistent with expectations in UK clinical practice. For these reasons, the health state costs in the original CS were informed by Morgan et al. 2024.

While Morgan et al. 2024 provides robust and comprehensive data on costs associated with primary care, prescriptions, outpatient appointments, A&E attendances, and inpatient admissions, we acknowledge the EAG's suggestion that additional costs, such as those for tertiary care or medical aids, may not be fully captured in this source. Landfeldt et al. 2014 includes costs related to these additional resource categories, as well as those covered in Morgan et al. 2024.[35] However, there are several limitations which make interpretations from this paper challenging:

- The data were collected in 2012–2013, making them outdated compared with the more recent and relevant data from Morgan et al. 2024.
- Landfeldt et al. 2014 do not provide a breakdown of costs by health state, limiting its applicability for a health-state model. Whilst this is provided in Landfeldt et al. 2017, the later paper does not provide a breakdown for non-medical community services, aids, devices, nor investments.[36]
- The paper lacks detailed information on costs comprising non-medical community services, medical aids, devices, and investments. As the data were collected via questionnaires completed by patients and their caregivers, the

figures potentially include out-of-pocket expenses that are not relevant for this appraisal.

We maintain that Morgan et al. 2024 provides the most robust data available. However, in response to this question, we have included an additional option in the updated CEM, titled “Givinostat CEM in DMD_NICE_PAS_CQ [CON].” This option combines the costs from Morgan et al. 2024 with a multiplier to account for the increased costs associated with non-medical community services, medical aids, devices, and investments as estimated from Landfeldt et al. 2014. This option is available on the “Cost data” sheet of the model. Whilst this is provided as a scenario in response to the EAG’s Clarification Question, we do not believe that these costs should inform base case decision-making. This is because a significant proportion of these costs, such as home adaptations, mobility aids, and specialised equipment, are directly borne by families rather than funded by the NHS or PSS. Additionally, many aids and devices are provided or subsidised by charities. Nevertheless, the impact of including these costs on the ICER is demonstrated below.

Landfeldt et al. 2014 present costs in 2012 US dollars, broken down by resource use category for patients residing in the United Kingdom (see Table 13 for details). These data allow us to identify the proportional increase in total costs when including non-medical community services, medical aids, devices, and investments compared to excluding these costs (+205.3%). This percentage reflects the relative contribution of these additional categories to the total costs. To estimate what the costs from Morgan et al. 2024 would look like if these categories were included, the +205.3% multiplier derived from Landfeldt et al. 2014 is applied to the health state costs from Morgan et al. 2024.

The resulting health state costs applied in the updated CEM compared to the original CS are presented in Table 14. Including the multiplier estimated from Landfeldt et al. 2014 to estimate the health state costs inclusive of non-medical community services, aids, devices, and investments increases the ICER from [redacted] to [redacted], representing a 2.5% increase (inclusive of the PAS) - Table 15.

This analysis has been provided to address the potential impact of including costs for non-medical community services, aids, devices, and investments, as highlighted by

the EAG. While it offers an estimate of these additional costs, it is important to note that the calculation relies on several assumptions and is subject to significant uncertainties.

**Table 13: Per-patient annual costs of DMD from the United Kingdom data in Table 2 in Landfeldt et al. 2014[35]**

| | **Costs (2012, international dollars)** |
|---|---|
| Hospital admissions | $2,300 |
| Visits to physicians and other health care practitioners | $8,230 |
| Tests and assessments | $1,580 |
| Medications | $930 |
| **Total excluding non-medical community services, aids, devices, and investments** | **$13,040** |
| Non-medical community services | $19,250 |
| Aids, devices, and investment | $7,520 |
| **Total including non-medical community services, aids, devices, and investments** | **$39,810** |
| Proportional increase in total costs including non-medical community services, aids, devices, and investments | 205.3% |

Abbreviations: DMD, Duchenne muscular dystrophy.

**Table 14: Direct medical health-state costs applied in the updated CEM**

| **Health states, N** | **Health states, description** | **Original CS** | **Updated including the multiplier to account for non-medical community services, aids, devices, and investments** |
|---|---|---|---|
| 1 | Early ambulatory | £3,298 | £10,068 |
| 2 | Late ambulatory | £3,298 | £10,068 |
| 3 | Transfer | £3,298 | £10,068 |
| 4 | HTMF, no ventilation | £6,681 | £20,397 |
| 5 | HTMF, night ventilation | £6,681 | £20,397 |
| 6 | No HTMF, no ventilation | £9,843 | £30,049 |
| 7a, 7b | No HTMF, night ventilation | £9,843 | £30,049 |
| 8a, 8b | Full ventilation | £9,843 | £30,049 |

Abbreviations: CEM, cost-effectiveness model; CS, Company submission; HTMF, hand-to-mouth function.

**Table 15: Clarification Question 9 | Scenario analysis with additional costs representing tertiary care, medical aids, and investments (with PAS)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc costs (£) | Inc LYG | Inc QALYs* | ICER (£/QALY)* |
|---|---|---|---|---|---|---|---|
| **Givinostat** | [redacted] | 21.9 | 19.3 | | | | |
| **ECM** | £286,991 | 14.6 | 6.1 | [redacted] | 7.3 | 22.4 | [redacted] |

*Including the 1.7 severity modifier.
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.

**B10. <u>Priority question:</u> We would like to request the PEDS-QL to EQ-5D mapping to be undertaken and added as an option to the company's economic model.**

**Response:** As detailed in Section B.2.6.6 and B.3.4.1 of the original CS, HRQoL is being assessed in the OLE study using the Pediatric Quality of Life Inventory (PedsQL) for paediatric patients and 36-item Short Form Health Survey (SF-36) for adult patients (at baseline, Week 48 and then yearly till the end of the study).[11]

In the original CS, it was stated that the PedsQL was not mapped to EQ-5D for use in the health economic modelling to avoid introducing additional uncertainty related to mapping algorithms. While we acknowledge the EAG's request for this analysis, there are additional reasons why it was not conducted, as detailed below.

Firstly, as outlined in the original CS, it is important to consider the high number of missing values when interpreting the PedsQL score results. These missing values were primarily due to site visits not being conducted during the COVID-19 pandemic.

Table 16 provides the number of responses recorded at baseline and through to month 72. The number of missing values, particularly across the longer follow-up measurements, limits the ability to estimate health state values over time for patients enrolled in the OLE.

**Table 16: Responses of PedsQL in the OLE | ITT population[11]**

| | N, responses |
|---|---|
| Baseline | 200 |
| Month 12 | 201 |
| Month 24 | 189 |
| Month 36 | 134 |
| Month 48 | 57 |
| Month 60 | 12 |
| Month 72 | 6 |

Abbreviations: ITT, intention to treat; N, number; OLE, open-label extension; PedsQL, Pediatric Quality of Life Inventory.

Source: DoF (Table 42, Study 51 Clinical Study Report; Dec 2023 DCO).[11]

Secondly, the two mapping algorithms (Khan et al. 2014 and Shafie et al. 2021) identified from the Dakin et al. 2023 HERC database which report on models mapping from PedsQL to EQ-5D are unsuitable for boys with DMD due to limited representation of relevant health states, high uncertainty in lower utility predictions, and limited overlap in population characteristics:[37–39]

- **Limited Representation of Relevant Health States**: In Khan et al. 2014, most patients had no mobility issues (94.8% scored level 1 in the EQ-5D mobility domain), no self-care issues (97.3% scored level 1 in the self-care domain), and no issues performing usual activities (93.5% scored level 1 in the usual activities domain). Similarly, in Shafie et al. 2021, most patients had no mobility issues (97.1% scored level 1 in the EQ-5D mobility domain), no self-care issues (95.7% scored level 1 in the self-care domain), and no issues performing usual activities (94.8% scored level 1 in the usual activities domain). These domains are impacted in boys with DMD, yet both datasets provide insufficient data to support mapping to EQ-5D levels 2 and 3 for these domains.
- **High Uncertainty in Lower Utility Predictions**: The lack of data for health states beyond level 1 leads to substantial uncertainty in predicting utilities for lower health states. This is evidenced by the relatively poor MSE and MAE observed for utilities below 0.6 in Khan et al. 2014 and by the conclusions in Shafie et al. 2021 stating that there were limited responses in the poorer quality of life scores, which resulted in poor estimation of utility scores below 0.8. Given

that neither algorithm can accurately estimate lower utility values, neither should be considered suitable to estimate utility for boys with DMD who will typically experience low utility values.

- **Limited Overlap in Population Characteristics**: The study population in Khan et al. 2014 was not limited to boys, and all patients were aged 11–15. The study itself acknowledges the uncertainty in the algorithm's ability to predict utilities for patients outside this narrow age range. The study population in Shafie et al. 2021 reflects transfusion-dependent thalassemia patients aged between 3 and 18 years – additionally, the study was conducted in Malaysia, and utilised the Malaysian EQ-5D-3L tariff value set. The study itself states that the mapping algorithm is relevant to a similar population. This further limits its applicability to the broader DMD population, which includes younger boys and older adolescents with differing disease progression.

Finally, even if the PedsQL data could be robustly mapped to the EQ-5D, these data would not provide a reliable basis for informing the CEM. This limitation arises from the reliance on assumptions and external sources to derive utility values for the later health states, for which there are limited or no observations from the OLE study. Such extrapolations would introduce significant uncertainty into the analysis, undermining the robustness of the results.

For these reasons, the PedsQL data from the OLE have not been mapped to the EQ-5D. Instead, we have maintained our original approach to modelling utilities based on Audhya et al. 2023.[40] This approach is well-supported and provides a robust framework for estimating patient utility values. Additionally, any potential uncertainty in these values has been thoroughly explored through scenario analyses using alternative sources and sensitivity analyses.

**B11.** Please clarify why the economic model does not explore a scenario mapping PODCI to EQ-5D. This was undertaken by Posner et al. 2024 using a longitudinal repeated measures model on 140 observations for 53 patients of DMD[b].

[b] https://www.sciencedirect.com/science/article/pii/S096089662400275X

Alternatively, the relationship between PODCI and PEDS-QL has been described in a study by McDonald et al. 2013[c] which could have been used to map to EQ-5D.

**Response:** HRQoL data were collected in the EPIDYS clinical trial at baseline, week 48, and week 72 using the Paediatric Outcomes Data Collection Instrument (PODCI).[1]

In the original CS, it was noted that no mapping algorithm exists to map PODCI to the EQ-5D. We appreciate the EAG bringing to our attention a published abstract describing a mapping algorithm from PODCI to EQ-5D in patients with DMD (Posner et al. 2024).[41] However, the information provided in this source is insufficient to perform the required mapping analysis. Furthermore, since the PODCI was only collected at baseline, week 48, and week 72, these data would not serve as a robust foundation for informing the CEM. This limitation arises from the need to rely on assumptions and external sources to estimate utility values for later health states or timepoints, for which EPIDYS provides limited or no observations.

In response to the suggestion of mapping PODCI to PedsQL and subsequently from PedsQL to EQ-5D, we refer to our clarification response B10, which explains why the two published mapping algorithms for PedsQL to EQ-5D are unsuitable for boys with DMD. In addition, the study by McDonald et al.[d] does not report regression coefficients so the results of the publication could not be applied to the givinostat data.[21] Additionally, if mapping was possible this approach would compound uncertainty from two separate mapping processes which can be subject to uncertainty. Therefore, this approach was not considered appropriate.

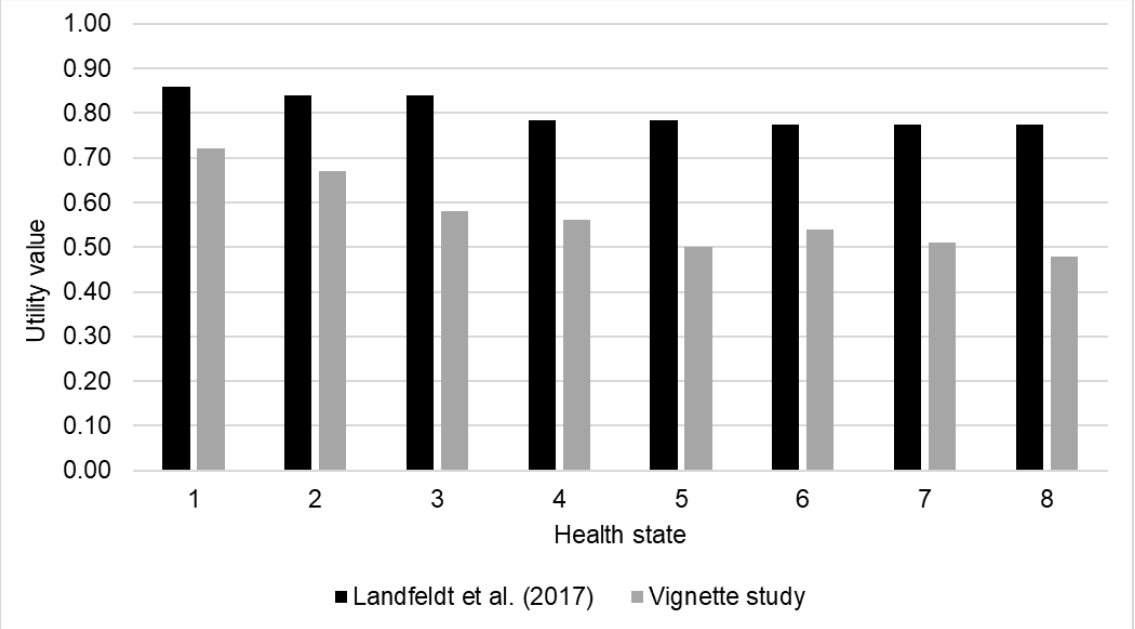
**B12.** Please can the company explain why care giver disutilities from the Vignette study are markedly higher in comparison to published studies? The EAG note that the NICE methods guide discourages the use of Vignette studies if other data sources are available.

**Response:** Figure 10 compares the caregiver utility values applied within the CEM as sourced from the Pfizer vignette study (base case) and Landfeldt et al. 2017 (scenario

[c] https://pmc.ncbi.nlm.nih.gov/articles/PMC3695468/
[d] https://pmc.ncbi.nlm.nih.gov/articles/PMC3695468/

analysis).[36,42] In line with the EAG's question, the utilities measured through the vignette study are consistently below those captured in Landfeldt et al. 2017.

**Figure 10: Comparison of caregiver utility values sourced from the Pfizer vignette study (base case) and Landfeldt et al. 2017 (scenario analysis)[36,42]**




The lower utility values derived from the vignettes compared to the EQ-5D are not unexpected and are thought to be more reflective of the HRQoL experienced by caregivers of patients with DMD – as justified below.

While the EQ-5D is a widely used and validated measure for HRQoL in economic evaluations, there are specific limitations in its application to caregivers of individuals with DMD, which the vignette approach overcomes:

1. Limited sensitivity to caregiver-specific burdens: the EQ-5D primarily focuses on physical and psychological domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). While valuable, it may not adequately capture the unique challenges faced by caregivers of people with DMD – as discussed in the literature - such as:[43–45]
    - Emotional and psychological stress specific to caregiving for a progressive and life-limiting condition.
    - Social and financial burdens, including impacts on work, education, and social interactions.

- Physical demands associated with caregiving, particularly in advanced stages of the disease.

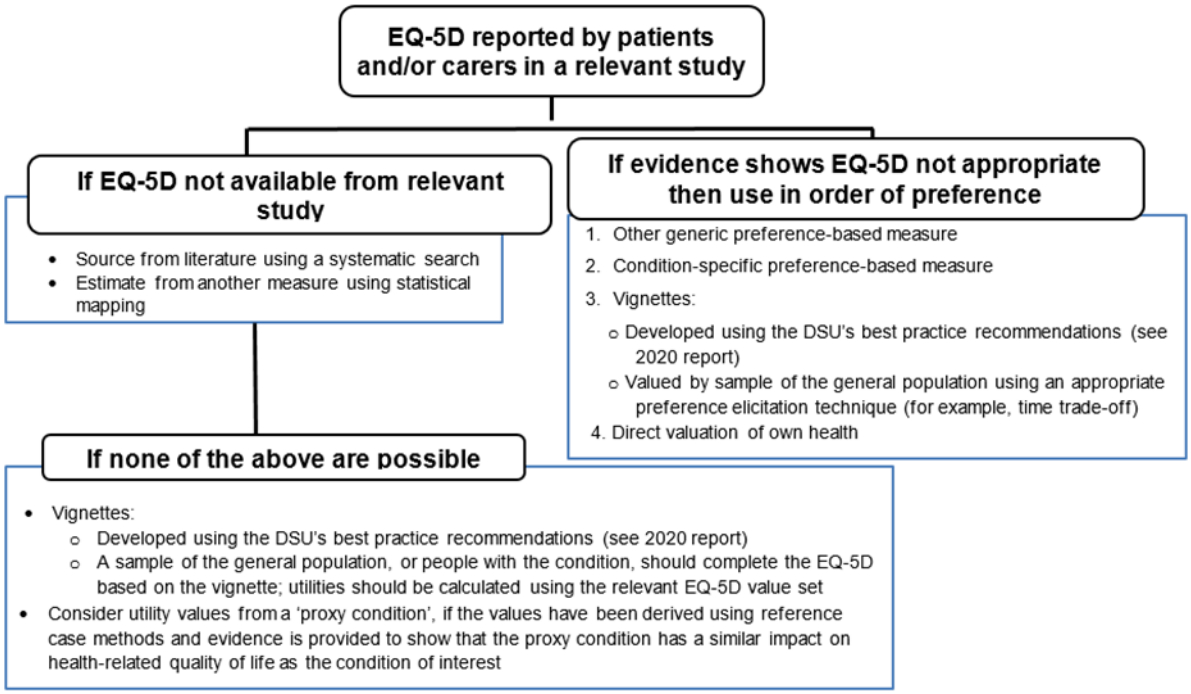
2. Limited sensitivity to health states: the EQ-5D struggles to capture nuanced differences in caregiver burden across health states. This issue is reflected in caregiver utility estimates from Landfeldt et al. 2017 which rely on EQ-5D data but fail to differentiate adequately between DMD health states (early/late ambulatory and non-ambulatory phases). The health states in the Project HERCULES CEM require an increased level of granularity not provided by existing caregiver utilities derived from EQ-5D data.

According to the NICE manual, when direct HRQoL data using EQ-5D is unavailable or inappropriate, alternative methods like vignette-based time trade-off (TTO) studies are recommended (Figure 11).[46] The vignette-based approach allows for the differentiation of utilities across detailed health states, reflecting the progression of DMD and its impact on caregivers. The higher specificity and granularity of vignettes lead to a more realistic representation of caregiver HRQoL. Additionally, the vignette study reflects a general population perspective; the vignette utilities reflect societal preferences, which are particularly relevant for health technology assessment and resource allocation decisions.

In the vamorolone NICE submission, the Company attempted to address the lack of specificity observed in the Landfeldt et al. 2017 study by using a blend of Landfeldt et al. 2017 utilities and data from a burden of illness (BOI) study to inform the base case caregiver utilities.[23,47] Further adjustments were made to account for the impact of behavioural issues on caregivers.

This approach, while an attempt to improve the accuracy of caregiver utilities, ended up being a somewhat flawed solution combining multiple data sources and leading to the Committee not being convinced that carer HRQoL had been modelled robustly. These challenges highlight the need for a more robust study of HRQoL in caregivers of individuals with DMD. We believe that our vignette study, conducted in line with published guidelines, provides a robust approach to capturing caregiver HRQoL.[48]

**Figure 11: Hierarchy of preferred health-related quality-of-life methods[46]**




Note: Figure taken from the NICE health technology evaluations manual
**Abbreviations**: DSU: Decision Support Unit

**B13. <u>Priority question:</u> Why did the company assume no caregiver QALYs are accrued in the ECM arm using the "increments relative to the midway health state approach"? This results in the discounted carers' QALYs increasing over time while the discounted patients' QALYS decreasing over time for the treatment arm. What publications if any describe "increments relative to the midway health state" methods used in the Company's base case?**

**Response:** Due to the limited guidance provided by NICE and international HTA bodies on how to model caregiver HRQoL, we raised this issue as a discussion point in the NICE Decision Problem meeting. The feedback from the attending EAG was that the burden of caregiving in DMD was well understood and accepted in previous appraisals. Therefore, the focus in our modelling should be on the impact of the new treatment (givinostat) on caregiver HRQoL compared to ECM. The attending EAG highlighted an approach that worked well in the NICE appraisal of mogamulizumab for previously treated mycosis fungoides and Sézary syndrome, as referenced in Section B.3.4.6 of the original CS.[49] In this appraisal, a utility gain for caregivers was included for the additional time patients in the mogamulizumab arm were able to remain in the "disease control" state, compared to those in the SOC arm i.e., utility increments were applied to the incremental QALYs in the less severe health states.

Following this feedback, and considering the literature which highlights challenges with historical approaches to modelling caregiver HRQoL (with no clear consensus on the best method), we applied increments or decrements relative to the midway health state approach to the incremental QALYs accrued by givinostat compared to ECM.[36,50–54] We believe this approach directly reflects the feedback from the attending EAG at the NICE Decision Problem meeting and the potential impact of givinostat on caregiver HRQoL.

Additionally, a presentation at HESG January 2025 considered the application and interpretation of the four approaches to modelling caregiver HRQoL that are considered as part of this appraisal: (1) caregiver utilities, (2) caregiver disutilities, (3) caregiver increments relative to the severe health state, and (4) caregiver increments relative to the midway health state.[55] This is part of ongoing research exploring different recommendations on the inclusion of caregiver utilities in CEMs.

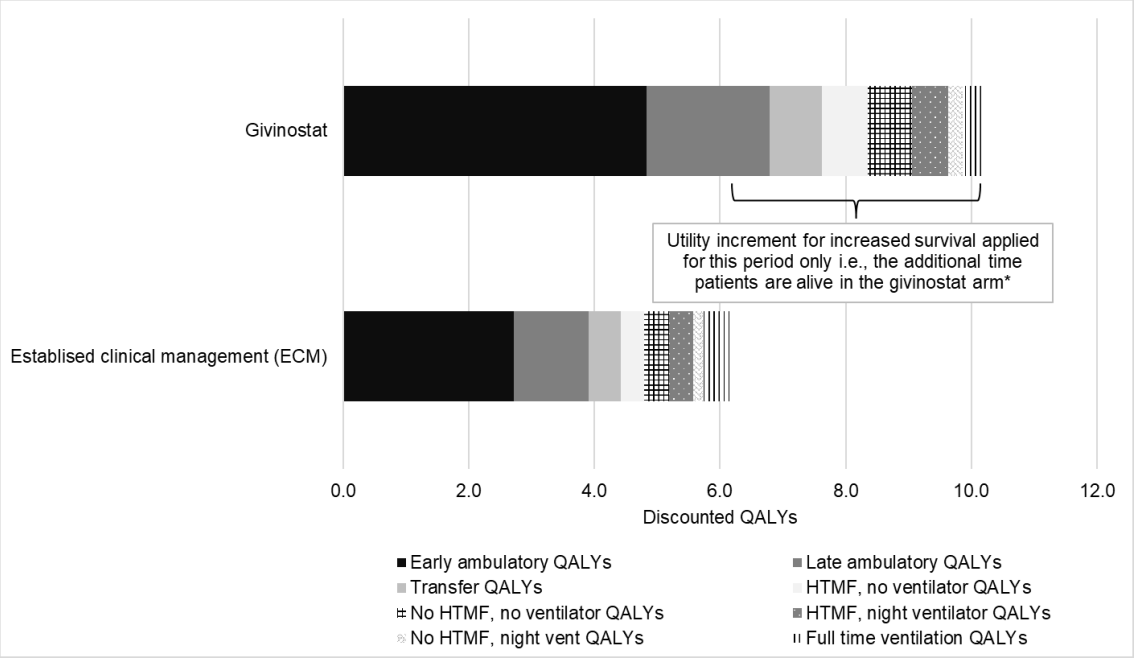
**B14.** Please clarify and discuss the bereavement disutility which is mentioned but not discussed in the CS. It is applied in 3 of the 4 methods for calculating carer quality of life and the magnitude of effect depends on the method chosen. In the company's base case the QALYs accrued for patients after death which under the company's base case makes up 90% of the discounted carer QALYs.

**Response:** Whilst the utility decrement applied in the caregiver disutilities approach can be interpreted as a bereavement disutility; it is a utility decrement applied from patient death for the remainder of the model time horizon. We believe there is a misunderstanding associated with the increment approaches (relative to the severe health state and relative to the midway health state approaches) and the utility decrement applied in the death health state. We would like to take the opportunity to clarify this.

In the increment approaches, the utility decrement associated with caregivers' experience of the death health state (shown in Table 67 of the original CS) is multiplied by the difference in the amount of time spent in the death health state for patients on givinostat compared to those on ECM. Since givinostat has the potential to be life-extending, patients on this treatment spend less time in the death health state compared to those on ECM. This means the difference in time is negative (less time in death), and when multiplied by the negative utility decrement associated with the

death health state, the result is a positive QALY gain (the result of a "double negative"). Therefore, the increment approaches do not apply a bereavement disutility, rather they apply an increment for the extension in survival relative to ECM. Importantly, this positive impact on caregiver HRQoL is only modelled for the additional survival time achieved with givinostat compared to ECM, not across the entire time horizon of the model – this is depicted in Figure 12. This distinction is crucial for accurately interpreting the results.

**Figure 12: A comparison of discounted QALYs by health state in the givinostat arm and the ECM arm and clarity of the application of the caregiver increment approaches**




*The CEM multiplies the utility decrement associated with caregivers' experience of the death health state by the difference in the amount of time spent in the death health state for patients on givinostat compared to those on ECM. Since givinostat is life-extending, patients on this treatment spend less time in the death health state compared to those on ECM. This means the difference in time is negative (less time in death), and when multiplied by the negative utility decrement associated with the death health state, the result is a positive utility increment (a "double negative").

Abbreviations: CEM, cost-effectiveness model; ECM, established clinical management; HTMF, hand-to-mouth function; QALY, quality adjusted life year.

In the Company base case, the impact of givinostat on caregiver HRQoL equates to an additional 4.59 QALYs (discounted) per caregiver. This reflects the increased time in ambulatory health states (12.40% of the QALY gain) and the increased time the patient is alive (88.58% of the QALY gain). This QALY gain is partially offset by the increased time in more severe health states for which caregiver HRQoL is assumed to be negatively affected. It is anticipated that the increased time in ambulatory health

states from givinostat relative to ECM will have a positive impact on caregiver HRQoL as these health states are associated with a reduced burden on the caregivers – as demonstrated by the literature.[36,42] However, it is also anticipated that the increased time a patient is alive from givinostat relative to ECM will have a positive impact on caregiver HRQoL. The extension in survival offers caregivers more time with a loved one, potentially reducing the anxiety of imminent loss and creating more opportunities for meaningful moments. The extra time can significantly alleviate or at the very least delay the emotional burden that comes from witnessing the decline of a loved one without hope. Whilst we acknowledge there are uncertainties underpinning the caregiver HRQoL approaches, we believe it is entirely plausible that the caregiver QALY gain associated with givinostat is driven by both the extension in patient survival and the prolonged duration in ambulatory health states.

**B15.** Please comment on the on the impact of the different methods for calculating carer quality of life? While it is true the methods do converge and the ICERs are the same, we've observed the rate at which discounted carer QALYs on treatment arm are accrued in the model does differ.

**Response:** The variation in caregiver QALY accrual across treatment arms arises from the differing approaches to modelling caregiver HRQoL.

Table 17 presents the incremental discounted caregiver QALYs by health state for each of the four modelling approaches: (1) caregiver utilities, (2) caregiver disutilities, (3) caregiver increments relative to the severe health state, and (4) caregiver increments relative to the midway health state. For clarity,

Table 17 reflects discounted caregiver QALYs for one caregiver. The base case assumes two caregivers, consistent with the original CS and the Committee's preferences in the vamorolone submission.[23]

**Table 17: Health state discounted caregiver QALYs across the different caregiver HRQoL modelling approaches**

| | Caregiver utilities | Caregiver disutilities | Caregiver increments relative to the severe health state | Caregiver increments relative to the midway health state |
|---|---|---|---|---|
| Early ambulatory QALYs | 1.92 | -0.54 | 0.64 | 0.43 |
| Late ambulatory QALYs | 0.81 | -0.31 | 0.23 | 0.13 |
| Transfer QALYs | 0.28 | -0.17 | 0.05 | 0.01 |
| HTMF, no ventilator QALYs | 0.73 | -0.47 | 0.10 | 0.00 |
| No HTMF, no ventilator QALYs | 0.64 | -0.54 | 0.03 | -0.08 |
| HTMF, night ventilator QALYs | 0.38 | -0.27 | 0.04 | -0.01 |
| No HTMF, night vent QALYs | 0.25 | -0.20 | 0.01 | -0.02 |
| Full time ventilation QALYs | -0.43 | 0.39 | 0.00 | 0.07 |
| Death | 0.00 | 6.70 | 3.48 | 4.07 |
| Total | **4.59** | **4.59** | **4.59** | **4.59** |

Abbreviations: HTMF, hand-to-mouth function; QALY, quality adjusted life years.

The caregiver utilities and disutilities approaches model caregiver HRQoL in both arms of the CEM. Incremental discounted caregiver QALYs are calculated as the difference in total caregiver QALYs accrued between the treatment arms. These approaches were included to align with case precedence and existing literature.[50,52] However, we do not believe that the QALY accrual under these methods reflects the dynamics of caregiver HRQoL in the DMD setting.

- **Caregiver Utilities Approach:** This method implies that caregivers experience a HRQoL benefit/worsening when patients remain in health states for longer/shorter periods due to treatment with givinostat relative to ECM. The method is primarily driven by differences in patient life years across health states. This approach fails to reflect the increased caregiving burden associated

with extended survival in the more severe health states. Nor does this approach reflect the impact on caregiver HRQoL associated with extended survival.

- **Caregiver Disutilities Approach:** This method implies that caregivers experience a HRQoL worsening/benefit when patients remain in health states for longer/shorter periods due to treatment with givinostat relative to ECM – this is the opposite effect implied by the caregiver utilities approach across living patient health states. A key inconsistency with this approach is that reduced time in the death state (i.e., longer survival) is assumed to improve caregiver HRQoL, contradicting the assumption that caregiving in living patient health states always worsens HRQoL.

The caregiver increments relative to the severe health state and caregiver increments relative to the midway health state characterise caregiver burden solely in terms of the additional impact on caregiver HRQoL from treatment with givinostat in the CEM.

- **Caregiver increments relative to the severe health state:** Caregiver HRQoL benefits are assumed for extended time in health states less severe than health state 8, i.e., the most severe living patient health state. No changes in HRQoL are modelled for health state 8, as it serves as the anchor point. This approach implies that caregiver benefits are driven by extended time in less severe health states and longer survival overall but does not account for variations in caregiving burden across earlier health states.
- **Caregiver increments relative to the midway health state:** This approach assumes caregiver HRQoL benefits are driven by extended time in health states 1–3 (before the loss of ambulation), with worsening HRQoL for increased time in health states 5–7. Reduced time in health state 8 results in an HRQoL improvement. No changes are modelled for health state 4, the anchor point. This method captures the dynamics of caregiving, as benefits are accrued during less severe health states, and burdens increase as caregiving demands grow in more severe health states.

As outlined in Section B.3.4.6 in the original CS, the caregiver increments relative to the midway health state approach aligns with expectations for caregiver HRQoL in DMD based on extended time in earlier health states (e.g., before loss of ambulation) improving caregiver HRQoL, and extended time in later health states (e.g., with loss

of upper limb function or independent lung function) worsens caregiver HRQoL. In addition to these health state-specific dynamics, the overall survival benefit from givinostat results in an improvement in caregiver HRQoL, consistent with real-world caregiving preferences.

Given the lack of a recommended method for modelling caregiver HRQoL, scenario analyses were included in the original CS (Section B.3.11.3) to explore the impact of all approaches. While each method reflects different accruals for caregiver QALYs, all approaches were shown to produce the same impact on the ICER, reducing uncertainty regarding the base case choice.

**B16.** Please modify the model to include a cost of a cost and disutility related the adverse event of prolonged QT interval. This is related to givinostat but was not mentioned in the EPIDYS trial. It is not seen in ECM.

**Response:** Modelling of the prolonged QT interval in the givinostat arm is not relevant as patients at increased risk of QT prolongation would not be treated with givinostat, in line with the SPC and the inclusion/exclusion criteria of the EPIDYS and OLE studies.[1,11,14] For patients eligible for treatment with givinostat, as represented by the EPIDYS and OLE populations, only one case of prolonged QT interval was flagged.

As outlined in Section B.2.9.1 of the original CS and the SPC, givinostat has the potential to cause QT interval prolongation. The SPC specifies that givinostat should not be used in patients at increased risk for ventricular arrhythmias, those with underlying cardiac disease, or those taking concomitant medications known to prolong the QT interval. Furthermore, the SPC recommends withholding givinostat if the QT interval exceeds 500 ms or if there is a change from baseline of more than 60 ms. The inclusion and exclusion criteria of the EPIDYS and OLE trials were aligned with these SPC recommendations. It is also expected that these guidelines will be adhered to in UK clinical practice.

In the EPIDYS trial, no QT interval prolongation was reported in either the givinostat or placebo groups. In the OLE trial, only one patient in the givinostat group experienced a QT change from baseline >60 ms with a QTc interval >450 ms at Month 40. Per the SPC, the treatment for such an event is to withhold givinostat. Since the

CEM already accounts for dose modifications, the management of this single prolonged QT interval event is already reflected in the modelling of costs.

**B17. <u>Priority question:</u> Please provide a scenario with higher costs and lower quality of life in the no HTMF and needing full ventilation states than in the no HTMF and night ventilation states (e.g., accounting for the proportion of patients needing full ventilation who have had a tracheostomy and thus need different ventilation kit; accounting for additional care needs of patients on full ventilation).**

**Response:** The health states referenced in the EAG's question pertain to health state 8 ("no HTMF with full ventilation") and health state 7 ("no HTMF with night ventilation"). In the base case CEM, the costs and patient utilities for these two health states are assumed to be identical. This assumption stems from limited data availability and a preference to derive all health state costs and utilities from a single source to reduce the uncertainty associated with combining multiple data sources. However, we acknowledge the validity concerns raised by the EAG in this question as the transition from “no HTMF with night ventilation” to “no HTMF with full ventilation” will cause an increase in both costs and burden on patient HRQoL. Therefore, in response to the EAG's query, a scenario analysis has been conducted using multipliers derived from the literature to adjust the costs and patient utilities for health state 8 relative to health state 7, as detailed below.

As detailed in Sections B.3.5.1 and B.3.5.3 of the original CS, the Project HERCULES CPRD study (Morgan et al. 2024) is the primary source of health state cost data for the base case.[34] This study, based on a UK-specific cohort of 639 patients, aligns with the NICE reference case by using NHS and PSS costs and reflects disease progression. However, its health states are less granular than those in the CEM, grouping costs into “ambulatory,” “non-ambulatory/no ventilation,” and “non-ambulatory/with ventilation.” Consequently, the costs for health states 7 and 8 are assumed equal to “non-ambulatory/with ventilation.”

The Project HERCULES UK BOI study is the only source distinguishing costs between health states 7 and 8, but it was excluded from the base case due to low patient numbers and concerns about data validity.[47] In response to the EAG’s question, a multiplier has been calculated from the UK BOI study reflecting the increase in costs

from health state 7 to health state 8 (1.3 = £10,506/£7,978). This is then applied to the "non-ambulatory/with ventilation" cost from the CPRD study, resulting in £12,962 for health state 8. This adjustment reflects the potential for increased costs associated with health state 8 relative to health state 7.

As outlined in Sections B.3.4.3 and B.3.4.6 of the original CS, Audhya et al. 2023 is the source of patient utility data for the base case.[40] This study uses EQ-5D, aligns with the NICE reference case, and provides the most recent patient HRQoL data in DMD. While the utility measurements generally correspond with the CEM health states, some health state utilities were estimated as weighted averages due to slight differences in health state definitions. This resulted in the same utility being assumed for health states 7 and 8 in the base case.

In response to the EAG's question, a multiplier has been calculated from Landfeldt et al. 2017 reflecting the reduction in patient utilities from health state 7 to health state 8 (0.6 = 0.051/0.129).[36] This is then applied to the patient utility in health state 7, resulting in a utility value of 0.06 for health state 8. This adjustment reflects the potential for reduced HRQoL in health state 8 compared to health state 7.

Including the multipliers differentiating health state costs and patient utilities for health state 8 and health state 7 using the methods described above decreases the ICER from [redacted] to [redacted], representing a 0.9% decrease (inclusive of the PAS). Note: this scenario can be implemented in the CEM using the drop-down selections on the "Cost data" and "HRQoL data" sheets, respectively.

**Table 18: Clarification Question 17 | Scenario analysis with differential health state costs and patient utilities for health state 8 vs. health state 7 (with PAS)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc costs (£) | Inc LYG | Inc QALYs* | ICER (£/ QALY)* |
|---|---|---|---|---|---|---|---|
| **Givinostat** | [redacted] | 21.9 | 19.1 | | | | |
| **ECM** | £107,876 | 14.6 | 5.9 | [redacted] | 7.3 | 22.5 | [redacted] |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.
*Including the 1.7 severity modifier

**B18.** Please update the BIM to capture the costs of spinal fusion, the values in cells BIM!F117:G121 of the confidential CEM are showing zero.

**Response:** As outlined in Section 4 of the original BI template, costs associated with scoliosis are not captured within the BIA time horizon. The values in cells BIM!F117:G121 show zero because no costs related to spinal fusion surgery are accrued within the BIA time horizon. According to data from McDonald et al. 2018, spinal fusion surgery typically occurs, on average, four years after the loss of ambulation, with eligibility for surgery limited to patients aged 15–25 years.[29] As a result, these costs fall outside the BIA time horizon. This exclusion reflects a cost-saving benefit anticipated with givinostat, which is not captured within the BIA results.

**B19.** For the OWSA, please provide justification for the assumption that the standard error will be 20% of the mean value. Please also provide a table/list of the inputs for which this assumption was needed. Finally, please point to the cell in the Excel model where this assumption can be varied.

**Response:** As stated in Section B.3.8 of the original CS, in the absence of data, the higher and lower values used in the OWSA were estimated based on a standard error (SE) of ±20% of the mean value. When information on lower and upper bounds is unavailable, a commonly accepted approach is to assume that the SE is a percentage of the mean, typically ranging from 10–20%.

In the CEM submitted as part of the original CS, a 20% SE was used to account for higher uncertainty within the OWSA. Table 19 details the parameters for which the SE was calculated using ±20% of the mean value and the corresponding lower and upper

bounds. This assumption generates plausible ranges for parameters where data on 95% confidence intervals are lacking.

We believe this approach aligns with the NICE manual's guidance to "assign distributions to characterise the uncertainty associated with the (precision of) mean parameter values".[46] Our method makes assumptions for the SE, but then incorporates this into a distribution suited to each parameter.

This approach differs from that taken in the vamorolone and ataluren NICE submissions, where the higher and lower values were calculated as ±15% and ±20% of the mean, respectively, without applying any distribution to reflect uncertainty. By incorporating distributions specific to each parameter, our approach provides a more robust and guideline-compliant representation of uncertainty.

The cell in the CEM in which the proportion of the mean value informing the SE can be changed is "M2" on the "Control" sheet.

**Table 19: Parameters informing the CEM for which the SE is calculated based on ±20% of the mean value.**

| Parameter name | Current value | Parameter distribution | SE (20% of mean) | Lower value of parameter | Upper value of parameter |
|---|---|---|---|---|---|
| Average weight: Age 4 | 17.5 | Normal | 3.5 | 10.6 | 24.4 |
| Average weight: Age 5 | 19.8 | Normal | 4.0 | 12.0 | 27.5 |
| Average weight: Age 6 | 22.0 | Normal | 4.4 | 13.4 | 30.6 |
| Average weight: Age 7 | 24.3 | Normal | 4.9 | 14.7 | 33.8 |
| Average weight: Age 8 | 27.0 | Normal | 5.4 | 16.4 | 37.6 |
| Average weight: Age 9 | 30.0 | Normal | 6.0 | 18.2 | 41.8 |
| Average weight: Age 10 | 33.0 | Normal | 6.6 | 20.1 | 45.9 |
| Average weight: Age 11 | 36.3 | Normal | 7.3 | 22.0 | 50.5 |
| Average weight: Age 12 | 40.5 | Normal | 8.1 | 24.6 | 56.4 |
| Average weight: Age 13 | 46.0 | Normal | 9.2 | 28.0 | 64.0 |
| Average weight: Age 14 | 52.5 | Normal | 10.5 | 31.9 | 73.1 |
| Average weight: Age 15 | 58.3 | Normal | 11.7 | 35.4 | 81.1 |
| Average weight: Age 16 | 62.8 | Normal | 12.6 | 38.2 | 87.3 |
| Average weight: Age 17 | 66.0 | Normal | 13.2 | 40.1 | 91.9 |
| Average weight: Age 18 | 83.6 | Normal | 16.7 | 50.8 | 116.4 |
| Average height: Age 4 | 106.0 | Normal | 21.2 | 64.4 | 147.6 |
| Average height: Age 5 | 113.0 | Normal | 22.6 | 68.7 | 157.3 |
| Average height: Age 6 | 119.0 | Normal | 23.8 | 72.4 | 165.6 |
| Average height: Age 7 | 125.0 | Normal | 25.0 | 76.0 | 174.0 |
| Average height: Age 8 | 131.0 | Normal | 26.2 | 79.6 | 182.4 |
| Average height: Age 9 | 136.0 | Normal | 27.2 | 82.7 | 189.3 |

| Parameter name | Current value | Parameter distribution | SE (20% of mean) | Lower value of parameter | Upper value of parameter |
|---|---|---|---|---|---|
| Average height: Age 10 | 141.0 | Normal | 28.2 | 85.7 | 196.3 |
| Average height: Age 11 | 146.0 | Normal | 29.2 | 88.8 | 203.2 |
| Average height: Age 12 | 151.0 | Normal | 30.2 | 91.8 | 210.2 |
| Average height: Age 13 | 159.0 | Normal | 31.8 | 96.7 | 221.3 |
| Average height: Age 14 | 166.0 | Normal | 33.2 | 100.9 | 231.1 |
| Average height: Age 15 | 171.0 | Normal | 34.2 | 104.0 | 238.0 |
| Average height: Age 16 | 175.0 | Normal | 35.0 | 106.4 | 243.6 |
| Average height: Age 17 | 177.0 | Normal | 35.4 | 107.6 | 246.4 |
| Average height: Age 18 | 178.0 | Normal | 35.6 | 108.2 | 247.8 |
| Givinostat hazard ratio: To state 2 - Late ambulatory | 0.51 | Log-normal | 0.10 | 0.42 | 0.62 |
| Givinostat hazard ratio: To state 3 - Transfer | 0.51 | Log-normal | 0.10 | 0.42 | 0.62 |
| Givinostat hazard ratio: To state 4 - HTMF, no ventilation | 0.51 | Log-normal | 0.10 | 0.42 | 0.62 |
| Givinostat hazard ratio: To state 5 - No HTMF, no ventilation | 0.39 | Log-normal | 0.08 | 0.33 | 0.45 |
| Givinostat hazard ratio: To state 7a - No HTMF, night-time ventilation | 0.39 | Log-normal | 0.08 | 0.33 | 0.45 |
| Givinostat hazard ratio: To state 8a - Full time ventilation | 0.46 | Log-normal | 0.09 | 0.39 | 0.55 |
| Givinostat hazard ratio: To state 6 - HTMF, night-time ventilation | 0.39 | Log-normal | 0.08 | 0.33 | 0.45 |
| Givinostat hazard ratio: To state 7b - No HTMF, night-time ventilation | 0.46 | Log-normal | 0.09 | 0.39 | 0.55 |
| Givinostat hazard ratio: To state 8b - Full time ventilation | 0.46 | Log-normal | 0.09 | 0.39 | 0.55 |
| Duvyzat® (givinostat) - Decreased platelet count - EPIDYS | 20.0 | Normal | 4.0 | 12.2 | 27.8 |
| Duvyzat® (givinostat) - Thrombocytopenia - EPIDYS | 19.0 | Normal | 3.8 | 11.6 | 26.4 |
| Duvyzat® (givinostat) - Increased blood triglyceride concentration - EPIDYS | 14.0 | Normal | 2.8 | 8.5 | 19.5 |
| Duvyzat® (givinostat) - Hyperglyceridaemia - EPIDYS | 13.0 | Normal | 2.6 | 7.9 | 18.1 |
| Duvyzat® (givinostat) - Diarrhoea - EPIDYS | 25.0 | Normal | 5.0 | 15.2 | 34.8 |
| Duvyzat® (givinostat) - Abdominal pain - EPIDYS | 16.0 | Normal | 3.2 | 9.7 | 22.3 |

| Parameter name | Current value | Parameter distribution | SE (20% of mean) | Lower value of parameter | Upper value of parameter |
|---|---|---|---|---|---|
| Duvyzat® (givinostat) - Upper abdominal pain - EPIDYS | 9.0 | Normal | 1.8 | 5.5 | 12.5 |
| Duvyzat® (givinostat) - Vomiting - EPIDYS | 7.0 | Normal | 1.4 | 4.3 | 9.7 |
| Duvyzat® (givinostat) - Decreased platelet count - Study 51 | 29.0 | Normal | 5.8 | 17.6 | 40.4 |
| Duvyzat® (givinostat) - Thrombocytopenia - Study 51 | 33.0 | Normal | 6.6 | 20.1 | 45.9 |
| Duvyzat® (givinostat) - Increased blood triglyceride concentration - Study 51 | 41.0 | Normal | 8.2 | 24.9 | 57.1 |
| Duvyzat® (givinostat) - Hyperglyceridaemia - Study 51 | 19.0 | Normal | 3.8 | 11.6 | 26.4 |
| Duvyzat® (givinostat) - Diarrhoea - Study 51 | 40.0 | Normal | 8.0 | 24.3 | 55.7 |
| Duvyzat® (givinostat) - Abdominal pain - Study 51 | 16.0 | Normal | 3.2 | 9.7 | 22.3 |
| Duvyzat® (givinostat) - Upper abdominal pain - Study 51 | 10.0 | Normal | 2.0 | 6.1 | 13.9 |
| Duvyzat® (givinostat) - Vomiting - Study 51 | 8.0 | Normal | 1.6 | 4.9 | 11.1 |
| Clinical management without givinostat - Decreased platelet count - EPIDYS | 0.0 | Normal | 0.0 | 0.0 | 0.0 |
| Clinical management without givinostat - Thrombocytopenia - EPIDYS | 0.0 | Normal | 0.0 | 0.0 | 0.0 |
| Clinical management without givinostat - Increased blood triglyceride concentration - EPIDYS | 3.0 | Normal | 0.6 | 1.8 | 4.2 |
| Clinical management without givinostat - Hyperglyceridaemia - EPIDYS | 1.0 | Normal | 0.2 | 0.6 | 1.4 |
| Clinical management without givinostat - Diarrhoea - EPIDYS | 2.0 | Normal | 0.4 | 1.2 | 2.8 |
| Clinical management without givinostat - Abdominal pain - EPIDYS | 2.0 | Normal | 0.4 | 1.2 | 2.8 |
| Clinical management without givinostat - Upper abdominal pain - EPIDYS | 1.0 | Normal | 0.2 | 0.6 | 1.4 |

| Parameter name | Current value | Parameter distribution | SE (20% of mean) | Lower value of parameter | Upper value of parameter |
|---|---|---|---|---|---|
| Clinical management without givinostat - Vomiting - EPIDYS | 0.0 | Normal | 0.0 | 0.0 | 0.0 |
| Givinostat: Time to surgery after loss of ambulation (years) | 4.0 | Log-normal | 0.8 | 0.8 | 19.2 |
| Established clinical management (ECM) % pts receiving spinal surgery | 0.4 | Beta | 0.1 | 0.2 | 0.5 |
| Established clinical management (ECM): Time to surgery after loss of ambulation (years) | 4.0 | Log-normal | 0.8 | 0.8 | 19.2 |
| Number of patients discontinued givinostat - EPIDYS | 7.0 | Normal | 1.4 | 4.3 | 9.7 |
| Number of patients discontinued givinostat - Study 51 | 21.0 | Normal | 4.2 | 12.8 | 29.2 |
| Number of patients discontinued established clinical management - EPIDYS | 2.0 | Normal | 0.4 | 1.2 | 2.8 |
| Givinostat compliance - EPIDYS | 1.0 | Beta | 0.2 | 0.8 | 1.0 |
| Givinostat compliance - Study 51 | 1.0 | Beta | 0.2 | 0.9 | 1.0 |
| Established clinical management compliance - EPIDYS | 1.0 | Beta | 0.2 | 0.8 | 1.0 |
| Givinostat number with dose modifications - EPIDYS | 86.0 | Normal | 17.2 | 52.3 | 119.7 |
| Givinostat number with dose reductions - EPIDYS | 57.0 | Normal | 11.4 | 34.7 | 79.3 |
| Givinostat number with dose temporarily stopped - EPIDYS | 19.0 | Normal | 3.8 | 11.6 | 26.4 |
| Givinostat number with dose skipped - EPIDYS | 47.0 | Normal | 9.4 | 28.6 | 65.4 |
| Givinostat number with dose increased - EPIDYS | 6.0 | Normal | 1.2 | 3.6 | 8.4 |
| Givinostat number with dose permanently stopped - EPIDYS | 10.0 | Normal | 2.0 | 6.1 | 13.9 |
| Givinostat number with dose modifications - Study 51 | 185.0 | Normal | 37.0 | 112.5 | 257.5 |
| Givinostat number with dose reductions - Study 51 | 84.0 | Normal | 16.8 | 51.1 | 116.9 |

| Parameter name | Current value | Parameter distribution | SE (20% of mean) | Lower value of parameter | Upper value of parameter |
|---|---|---|---|---|---|
| Givinostat number with dose temporarily stopped - Study 51 | 69.0 | Normal | 13.8 | 42.0 | 96.0 |
| Givinostat number with dose skipped - Study 51 | 83.0 | Normal | 16.6 | 50.5 | 115.5 |
| Givinostat number with dose increased - Study 51 | 145.0 | Normal | 29.0 | 88.2 | 201.8 |
| Givinostat number with dose permanently stopped - Study 51 | 21.0 | Normal | 4.2 | 12.8 | 29.2 |
| Established clinical management number with dose modifications - EPIDYS | 28.0 | Normal | 5.6 | 17.0 | 39.0 |
| Established clinical management number with dose reductions - EPIDYS | 7.0 | Normal | 1.4 | 4.3 | 9.7 |
| Established clinical management number with dose temporarily stopped - EPIDYS | 6.0 | Normal | 1.2 | 3.6 | 8.4 |
| Established clinical management number with dose skipped - EPIDYS | 24.0 | Normal | 4.8 | 14.6 | 33.4 |
| Established clinical management number with dose increased - EPIDYS | 6.0 | Normal | 1.2 | 3.6 | 8.4 |
| Established clinical management number with dose permanently stopped - EPIDYS | 1.0 | Normal | 0.2 | 0.6 | 1.4 |
| Patient utilities: Audhya et al. 2023 - 6 - HTMF, night-time ventilation | 0.3 | Beta | 0.1 | 0.2 | 0.4 |
| Number of caregivers | 2.0 | Normal | 0.4 | 1.2 | 2.8 |
| Spinal fusion surgery: Disutility | 0.1 | Beta | 0.0 | 0.0 | 0.1 |
| Spinal fusion surgery: Duration of disutility (years) | 1.0 | Normal | 0.2 | 0.6 | 1.4 |
| Decreased platelet count: Disutilities | 0.0 | Beta | 0.0 | 0.0 | 0.0 |
| Thrombocytopenia: Disutilities | 0.0 | Beta | 0.0 | 0.0 | 0.0 |
| Increased blood triglyceride concentration: Disutilities | 0.0 | Beta | 0.0 | 0.0 | 0.0 |
| Hyperglyceridaemia: Disutilities | 0.0 | Beta | 0.0 | 0.0 | 0.0 |
| Diarrhoea: Disutilities | 0.0 | Beta | 0.0 | 0.0 | 0.1 |

| Parameter name | Current value | Parameter distribution | SE (20% of mean) | Lower value of parameter | Upper value of parameter |
|---|---|---|---|---|---|
| Abdominal pain: Disutilities | 0.0 | Beta | 0.0 | 0.0 | 0.1 |
| Upper abdominal pain: Disutilities | 0.0 | Beta | 0.0 | 0.0 | 0.1 |
| Vomiting: Disutilities | 0.1 | Beta | 0.0 | 0.1 | 0.1 |
| Decreased platelet count: Duration of event (days) | 30.4 | Normal | 6.1 | 18.5 | 42.4 |
| Increased blood triglyceride concentration: Duration of event (days) | 30.4 | Normal | 6.1 | 18.5 | 42.4 |
| Diarrhoea: Duration of event (days) | 30.4 | Normal | 6.1 | 18.5 | 42.4 |
| Abdominal pain: Duration of event (days) | 30.4 | Normal | 6.1 | 18.5 | 42.4 |
| Upper abdominal pain: Duration of event (days) | 30.4 | Normal | 6.1 | 18.5 | 42.4 |
| Vomiting: Duration of event (days) | 30.4 | Normal | 6.1 | 18.5 | 42.4 |
| Price / pack (£) - Prednisone | £8.51 | Gamma | £1.70 | £5.51 | £12.16 |
| Price / pack (£) - Prednisone | £55.08 | Gamma | £11.02 | £35.65 | £78.68 |
| Price / pack (£) - Deflazacort | £15.82 | Gamma | £3.16 | £10.24 | £22.60 |
| Spinal fusion surgery - Cost per unit (£) - Spinal surgery cost | £27,035 | Gamma | £5,407 | £17,496 | £38,617 |
| Spinal fusion surgery - Cost per unit (£) - Surgery follow-up | £5,539 | Gamma | £1,108 | £3,584 | £7,911 |
| Spinal fusion surgery - Cost per unit (£) - Indirect | £24,802 | Gamma | £4,960 | £16,051 | £35,427 |
| Spinal fusion surgery - Units per patient - Spinal surgery cost | £1.00 | Normal | £0.20 | £0.61 | £1.39 |
| Spinal fusion surgery - Units per patient - Surgery follow-up | £2.00 | Normal | £0.40 | £1.22 | £2.78 |
| Adverse event costs - Decreased platelet count | £0.00 | Gamma | £0.00 | £0.00 | £0.00 |
| Adverse event costs - Thrombocytopenia | £0.00 | Gamma | £0.00 | £0.00 | £0.00 |
| Adverse event costs - Increased blood triglyceride concentration | £0.00 | Gamma | £0.00 | £0.00 | £0.00 |
| Adverse event costs - Hyperglyceridaemia | £0.00 | Gamma | £0.00 | £0.00 | £0.00 |
| Adverse event costs - Diarrhoea | £0.41 | Gamma | £0.08 | £0.27 | £0.59 |
| Adverse event costs - Abdominal pain | £3.31 | Gamma | £0.66 | £2.14 | £4.73 |

| Parameter name | Current value | Parameter distribution | SE (20% of mean) | Lower value of parameter | Upper value of parameter |
|---|---|---|---|---|---|
| Adverse event costs - Upper abdominal pain | £3.31 | Gamma | £0.66 | £2.14 | £4.73 |
| Adverse event costs - Vomiting | £4.61 | Gamma | £0.92 | £2.98 | £6.59 |
| Direct medical costs by health state (CPRD) - 1 - Early ambulatory | £2,931 | Gamma | £586 | £1,897 | £4,187 |
| Direct medical by health state (CPRD) - 2 - Late ambulatory | £2,931 | Gamma | £586 | £1,897 | £4,187 |
| Direct medical by health state (CPRD) - 3 - Transfer | £2,931 | Gamma | £586 | £1,897 | £4,187 |
| Direct medical by health state (CPRD) - 4 - HTMF, no ventilation | £5,938 | Gamma | £1,188 | £3,843 | £8,482 |
| Direct medical by health state (CPRD) - 5 - No HTMF, no ventilation | £5,938 | Gamma | £1,188 | £3,843 | £8,482 |
| Direct medical by health state (CPRD) - 6 - HTMF, night-time ventilation | £8,748 | Gamma | £1,750 | £5,661 | £12,496 |
| Direct medical by health state (CPRD) - 7 - No HTMF, night-time ventilation | £8,748 | Gamma | £1,750 | £5,661 | £12,496 |
| Direct medical by health state (CPRD) - 8 - Full time ventilation | £8,748 | Gamma | £1,750 | £5,661 | £12,496 |

**B20. <u>Priority question:</u> Why was SOLVER used to fit hazard ratios instead of more formal approaches such as maximum likelihood estimation? The company could have written a likelihood based on the NHM transition probabilities and givinostat hazard ratios with 'data' from the MAIC-weighted givinostat data for median time to loss of ambulation, non-invasive ventilation, and FVC<1L. Maximising this likelihood would give estimated HRs and error estimates. This could also (potentially more easily) be done in the Bayesian framework with vague priors on the (log) hazard ratios.**

**Response:** As described in Section B.3.3.1 and B.3.3.2 of the original CS, the SOLVER functionality was implemented in Microsoft Excel to:

1. Estimate the HR required in the natural history model (NHM) to ensure the proportion surviving at 50-years aligned with 2.8% (updated NHM [analysis 1]).

2. Estimate the HRs required in the NHM to ensure that the median age at loss of ambulation aligned with 12.1 years and the proportion surviving at 50-years aligned with 2.8% (updated NHM [analysis 2], base case).

3. Estimate the HRs required in the givinostat arm relative to the ECM arm such that the predicted median age at loss of ambulation in the givinostat arm aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat loss of ambulation data.

4. Estimate the HRs required in the givinostat arm relative to the ECM arm such that the predicted median age at non-invasive ventilation in the givinostat arm aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat non-invasive ventilation data.

5. Estimate the HRs required in the givinostat arm relative to the ECM arm such that the predicted median age at age at FVC<30% in the givinostat arm aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat age at FVC<1L data.

We used SOLVER because it was considered a transparent and user-friendly tool. It allowed for the straightforward incorporation of constraints into the optimisation problem and avoided the need for assumptions about the underlying data. Additionally, we believed that using a widely recognised and accessible tool like SOLVER would make the calculations and outputs easier for others to follow and validate.

In response to Clarification Question B5 and the feedback received during the NICE Clarification Call, we recognise that the SOLVER calculations were not as transparent to the EAG as we had initially hoped. We have addressed this in our response to Clarification Question B5 and trust that the additional clarification resolves any remaining concerns.

The uncertainty in the model parameters was assessed through OWSA, where each variable, including the HRs, was independently varied based on 95% confidence intervals. For the HRs, the OWSA assumed a standard error equal to ±20% of the mean value and a log-normal distribution. Using these assumptions, the 95% confidence intervals were estimated. The resulting confidence intervals applied in the OWSA for HRs are detailed in Table 19 in the response to Clarification Question B19.

As described in the response to Clarification Question B19, a 20% SE was used to account for higher uncertainty within the OWSA.

More complex approaches, such as MLE, were not pursued because they require explicit assumptions about the data. Unfortunately, the UK real-world data informing the CEM are based on published sources with limited available information. MLE requires the correct specification of the likelihood function, which assumes a specific data distribution and can be challenging to define in the presence of relatively small sample sizes. If this assumption is mis-specified, it could lead to biased or inconsistent results. Given these considerations, we felt that using such complex methods might introduce additional uncertainty and reduce the transparency of the results.

**B21.** Can you please update the economic model to allow PSA and sensitivity analysis to run without restoring the default settings.

**Response:** As per the EAG's request, this functionality has been removed from the CEM.

**B22.** Please discuss the assumptions used for the calculating the absolute short fall in QALYs and severity modifier. Replicating the analysis[e] using the assumptions described in Table 85; for patients aged 6, 100% male and using 3.5% discount rate, the QALYs without disease are 24.69. Assuming 6.1 QALYs on ECM, the absolute shortfall in QALYs is 18.59 and the severity modifier is 1.7x. The results are sensitive to the method of calculating carer QALYs.

**Response:** The QALY Shortfall Calculator referenced in the EAG's question does not account for the time-varying discount rate applied in the Company's base case. This calculator, published by the University of York, is available through the R Shiny software – within which it is impossible for the user to integrate time-varying discount rates.

The Company has included the QALY shortfall calculations directly within the CEM on the "QALY Shortfall" sheet, based on the QALY Shortfall Calculator developed by the University of Sheffield – as referenced in NICE TSD 23.[56] This calculator, provided as an Excel file, aligns with the format of the CEM. This approach enhances transparency, as model inputs required for the QALY shortfall calculations are directly

[e] https://shiny.york.ac.uk/shortfall/

linked through the CEM. Any changes in the model inputs are instantly reflected in the QALY shortfall calculations. Furthermore, this method accommodates the time-varying discount rate for health outcomes. As outlined in Section B.3.2.2 of the original CS, health outcomes are discounted at 3.5% per annum for the first 30 years, followed by 1.5% per annum thereafter. Further clarification on this approach is provided in the response to Clarification Question B23.

To reassure the EAG that the calculations in the CEM align with the QALY Shortfall Calculator available through the University of York and the R Shiny application, additional analyses were conducted using the assumptions described in Table 85 of the original CS (i.e., patients aged six, 100% male, and 6.1 QALYs on ECM). Following this, a 3.5% discount rate for health outcomes was applied across the entire model time horizon in both the R Shiny app and the CEM. The absolute and proportional shortfalls calculated using both sources were identical: 18.61 and 75.37%, respectively.

This shows that the calculations underpinning all sources for estimating the QALY shortfall are consistent. However, when incorporating the time-varying discount rate from the Company's base case and applying non-reference discounting, the absolute and proportional shortfalls for patients relevant to this submission are 29.1 and 82.6%, respectively, as detailed in Section B.3.7 of the original CS.

Regardless of the approach to modelling discount rates, givinostat satisfies the criteria for the severity modifier of 1.7 as outlined in NICE TSD 23 i.e., an absolute QALY shortfall of at least 18.

**B23. <u>Priority question:</u> As reported in Table 37, the vamorolone and ataluren NICE appraisals use a 3.5% discount rate for the whole time horizon as base case, as do the hypothetical models of Landfeldt 2017 and Broomfield 2024. Please clarify why a 1.5% discount rate for benefits beyond 30 years (and indeed a 1.5% discount rate for benefits for the whole time horizon) would be more appropriate for givinostat than for vamorolone or ataluren.**

**Response:** In the original CS (Section B.3.2.2), we applied a 3.5% discount rate to health outcomes for the first 30 years, followed by a 1.5% discount rate, in line with the guidance from the HM Treasury Green Book.[57] The Green Book specifically states

that the discount rate for QALYs should reduce to 1.5% per annum when evaluating therapies with benefits extending over 30 years. Although the discount rates used in the base case deviate from the NICE reference case, we believe that the 1.5% discount rate is highly relevant and appropriate for this submission. In relation to the EAG's question, we believe that it is more relevant for givinostat than for the therapies evaluated in previous NICE submissions in DMD, including vamorolone and ataluren, due to the long-term benefits expected with givinostat and the currently available NICE processes and guidelines.

Firstly, givinostat meets two of the three criteria specified in the NICE Manual for non-reference discounting:

1. It is intended for a condition that severely impairs quality of life.

2. The benefits of givinostat are expected to be sustained over a long period, potentially extending well beyond 30 years.

While givinostat does not restore patients to full or near-full health (the third criterion), it significantly extends the period during which patients maintain earlier, less severe health states, which are associated with improved HRQoL.

Secondly, although not used in the base case, both the vamorolone and ataluren NICE submissions acknowledged the relevance of the 1.5% discount rate for health outcomes, with each exploring it in key scenario analyses:

- **Vamorolone NICE Submission**: A 1.5% discount rate was explored in scenario analyses for both costs and QALYs across the entire model time horizon.[23]

We disagree with the approach of applying a 1.5% discount rate to costs; as discussed in the HM Treasury Green Book a 3.5% discount rate for costs is appropriate to account for inflation over time.

Additionally, we believe that the 1.5% rate for health outcomes is more relevant to givinostat than to vamorolone. Givinostat has the potential to deliver benefits extending over 30 years (as demonstrated by the data in Section B.2.8 of the original CS), which aligns with the criteria outlined in the HM Treasury Green Book for applying

the 1.5% discount rate to health outcomes. This also aligns with one of the criterion specified in the NICE Manual for a non-reference discount rate. This contrasts with the vamorolone NICE submission, where the Committee's conclusions on efficacy indicated that while vamorolone improved muscle-function outcomes compared to placebo, no robust evidence was provided to suggest that vamorolone was equivalent to prednisone.

- **Ataluren NICE Submission**: A 1.5% discount rate was also explored in scenario analyses for health outcomes across the model time horizon.[8]

Since the ataluren submission began, there have been significant updates to the NICE processes and guidelines, including the publication of the updated NICE Manual in 2023 (with new non-reference discount rate criteria) and the introduction of new HST criteria in 2022. The criteria for non-reference discounting were unavailable at the time of the ataluren submission. However, two of the three criteria for non-reference discounting overlap with the old HST criteria: "the condition is chronic and severely disabling" and "the technology can be used for life." Ataluren was considered to meet these criteria, in addition to other factors, which routed it to the HST pathway.

Although they follow different approaches, both the HST process and the non-reference discounting within the standard STA process provide increased flexibility for conditions that severely impair quality of life and treatments expected to deliver sustained benefits.

In summary, both the vamorolone and ataluren NICE appraisals acknowledged the relevance of the 1.5% discount rate for health outcomes. However, we believe that givinostat meets the current criteria for non-reference discounting more directly than either of these treatments. As a conservative approach, we applied the 1.5% discount rate starting from 30 years in the base case, in line with the HM Treasury Green Book. However, as highlighted in Section B.3.11.3 of the original CS, this is a conservative approach and the scenario analysis assuming the 1.5% discount rate for health outcomes across the entire model time horizon (which results in a reduction in the ICER of -18.9% [from [redacted] with PAS to [redacted]]) may be more relevant for decision-making.

# Section C: Textual clarification and additional points

## *Company Systematic Literature Review*

**C1. <u>Priority question:</u> We have not located the protocol for the systematic review of clinical effectiveness, please can you provide it? Please also be clear about any possible post protocol amendments, if made.**

**Response:** Please see the protocol documents for both the original SLR and the SLR update that we have submitted alongside these responses. The file names are:

- ID6323_Givinostat-for-DMD_HTA-SLR-protocol_FINAL_240513
- ID6323_Givinostat-for-DMD_HTA-SLR-Q4-2024-update_Protocol_FINAL_241021

One protocol amendment was made following protocol finalisation. In the NICE final scope inclusion and exclusion eligibility criteria (Table 8 in the original protocol and Table 9 in the update protocol) we listed a comparator as 'established clinical management without givinostat from multinational or UK natural history studies' in the original SLR protocol and 'established clinical management without givinostat from UK natural history studies' in the update SLR protocol. This should have been included in the 'intervention' row, and the 'comparators' should have been 'any'. The Company screened as if it was an 'intervention' and therefore amended the table during write up to reflect the criteria used during screening.

**C2. <u>Priority question:</u> The searches for clinical effectiveness include Ataluren, as per the NICE scope. However, the company exclude ataluren from the submission and it is not included in the clinical SLR or in your submission. Please can you explain why you searched for studies reporting Ataluren but have not included studies in the review or submission?**

**Response:** The clinical SLR was conducted to support multiple reimbursement submissions for givinostat across markets, including for the current NICE appraisal. Ataluren, amongst many other DMD treatments, was therefore included in the search strings as part of a global clinical review that was designed to be comprehensive of all *potential* comparators for DMD. Consistent with typical practice for adaptation of global

SLRs to meet the needs of NICE appraisals, a final dual-screening step was conducted using the adapted eligibility criteria shown in Appendix Table 8 to align the SLR outputs with the final decision problem. This ensured that the final list of included studies only included evidence relevant to the decision problem.

Prior to conducting the original SLR, the potential availability of natural history data for established clinical management without givinostat was unclear. We therefore took a broad approach to identifying potential sources of real-world natural history data that included both multinational and UK natural history studies. These included, for example, the STRIDE and CINRG datasets. Assessment of the real-world studies identified by the review showed that there were sources of UK natural history data that were anticipated to better reflect outcomes for boys and men with DMD in the UK.

Subsequently, an update to the SLR was conducted in November 2024, to ensure that searches had been conducted within 6 months of submission. The eligibility criteria used are shown in Appendix Table 9. At this time, the Company had concluded that ataluren was not a relevant comparator for givinostat, primarily owing to the uncertainty surrounding its continued use in clinical practice following the EMAs confirmation of a non-renewal recommendation of the conditional marketing authorisation by the CHMP in January 2024.[5] The EAG is correct that ataluren could have been removed from the searches at this point. The Company remains confident that the appropriate clinical evidence has been identified in this review.

The Company also maintains its position that ataluren is not a relevant comparator for this appraisal. First, having concluded that the totality of the evidence showed a negative benefit-risk balance, in June 2024 the EMA recommended that the marketing authorisation for ataluren should not be renewed.[7] At the request of the Company, the CHMP re-examined the available data and in October 2024 concluded that the effectiveness of ataluren could not be confirmed. A non-renewal recommendation has been sent to the European Commission for a legally binding decision.[7] The Company is not aware of any information in the public domain about a reappraisal of ataluren by the MHRA (although several patient groups have mentioned the MHRA has begun its

own review),[fgh] but considers that the use of ataluren as part of routine NHS clinical practice for the treatment of DMD may become uncertain during the appraisal of givinostat, particularly since its orphan registration expired in August 2024.[58]

Finally, a direct cost comparison with ataluren would not be possible due to process differences between the HST (ataluren) and STA (givinostat) evaluations. Ataluren is only approved for use in a small subgroup of ambulatory patients who have a nonsense mutation in the dystrophin gene,[4] accounting for approximately 10–15% of boys and young men with DMD.[6]

**C3. <u>Priority question:</u> In the CS Appendices, Table 7 (page 29), criteria for outcomes eligible for inclusion states 'included but not limited to'. If the SLR protocol (requested in C1) does not include a specific list of prospectively eligible outcomes, please can the company provide a more specific list of outcomes considered relevant for inclusion in the SLR to ensure that bias was minimised in the process of review. Please also be clear about any possible post protocol amendments, if made.**

**Response:** Thank you for drawing our attention to the above wording. The Company would first like to reassure the EAG that we are confident that the outcomes captured in the inclusion criteria in Appendix Table 7 are the key outcomes relevant to the ITC and economic model, and therefore to assessing the added value givinostat brings to boys with DMD.

As has been flagged by the EAG in C4 below, there are some slight differences between the wording in the NICE scope and the outcome criteria listed in our review. We have discussed the specifics in more detail in the response to C4. The outcomes criteria specified in the review protocols are based on wording that matches what is more frequently used in clinical studies for DMD and are of relevance to the mechanism of action of givinostat. The protocol included the wording, **'included but not limited to'**, to give some flexibility to include outcomes even if the exact wording in the PICOS was not present. It also meant that studies using other measures of the outcomes could still be included. For example, under 'walking ability' and 'ambulation'

[f] European Medicine Agency's Committee for Medicinal Products for Human Use Issues Negative Opinion on Translarna Following European Commission Request for Review - Muscular Dystrophy UK
[gg] EMA's negative decision on Translarna upheld | Duchenne UK
[h] MHRA Translarna Survey - Action Duchenne

we were able to capture ‘loss of function’ in several studies. All outcomes utilised in the ITC and the economic model were clearly defined in the SLR protocols, and the Company is confident that the appropriate clinical evidence has been identified in this review.

**C4**. In Table 1, below (Page 18), we compare the NICE final scope to the inclusion criteria of the SLR. We highlight in yellow outcomes which are listed in the NICE scope but which do not obviously map to outcome criteria in your review of clinical effectiveness. Please can you confirm that the outcomes from the NICE scope are captured by outcomes in your inclusion criteria (highlighted in yellow). If not, please can you comment on why outcomes reported in the NICE scope were not included in the SLR informing your submission**.**

**Response:** Thank you for the opportunity to clarify the rationale behind the inclusion criteria outcomes. The included outcomes that correspond to the ones highlighted by the EAG are shown in Table 20.

**Table 20: Correlation of queried endpoints in the final NICE scope vs. the SLR protocol**

| Queried outcome | Associated SLR endpoints |
|---|---|
| Muscle function | • 4SC<br>• Walking ability (ambulation), e.g. using the 6MWT or 10-meter walking test<br>• Time to rise<br>• Ambulation, e.g. using time to wheelchair, NSAA, or number of falls<br>• Muscle strength, e.g. using **hand-to-mouth function**, knee flexion or extension, elbow flexion or extension<br>• Cardiac function, e.g. using ECG or ECHO<br>• Lung function, e.g. FVC<br>• Time to scoliosis |
| Ability to undertake activities of daily living | • 4SC<br>• Walking ability (ambulation), e.g. using the 6MWT or 10-meter walking test<br>• Time to rise<br>• Ambulation, e.g. using time to wheelchair, NSAA, or number of falls<br>• Muscle strength, e.g. using **hand-to-mouth function**, knee flexion or extension, elbow flexion or extension |
| Lower body function | • 4SC |

| Queried outcome | Associated SLR endpoints |
|---|---|
| | • Walking ability (ambulation), e.g. using the 6MWT or 10-meter walking test<br>• Time to rise<br>• Ambulation, e.g. using time to wheelchair, NSAA, or number of falls<br>• Muscle strength, e.g. using **hand-to-mouth function**, knee flexion or extension, elbow flexion or extension |
| Upper body function | • Muscle strength, e.g. using **hand-to-mouth function**, knee flexion or extension, elbow flexion or extension |
| Bone function<br><br>Concordance and optimisation of treatment<br><br>Endocrine function | • Outcome not included in SLR. Please see commentary below for rationale. |

The rationale for excluding endocrine function, bone function and concordance and optimisation of treatment was that these are not relevant to the mechanism of action of givinostat. Of note, none of these endpoints were included in the previous NICE assessment of ataluren (HST22); they were however included in the assessment of vamorolone (TA1031). Vamorolone is a modified steroid and, as such, the endpoints highlighted are relevant for an appraisal as they are well-established side effects of steroids,[59] and the impact of any medicine on these endpoints may lead to treatments modifications. The Company believes that, while these are important endpoints for the vamorolone assessment (TA1031), they are not relevant for the mechanism of action of givinostat.

**C5.** In the review of clinical effectiveness (Appendices, D.1.4., page 33), you report: *"Data were extracted by one reviewer and spot-checked for quality by a second reviewer; if necessary, discrepancies were reconciled by a third reviewer."* Please can you explain what 'spot-checked' means, and how many/ what proportion of records were 'spot-checked'? If you did not check all records, please can you explain why?

**Response:** For this SLR we prioritised data extraction for all the givinostat studies, and the studies being used in the ITC (i.e., RWE). All these studies were extracted by two people in parallel, with a third reviewer on hand to resolve discrepancies. For the

remaining papers that were not going to form key parts of the evidence base, but had been identified in the SLR, it was considered appropriate to check 20-40% of the extracted data to ensure extraction accuracy. This targeted approach was considered appropriate due to ongoing dialogue with the statisticians conducting the ITC.

**C6.** The SLR uses the tool reported in the CRD handbook to quality appraise randomised studies. The Cochrane Risk of Bias tool (RoB 2) provides a more robust assessment of potential biases, by outcome and not at the study level. Please can you repeat the quality appraisal using RoB 2?

**Response:** Please see Table 21 and Table 22 below for an appraisal of the relevant endpoints in the EPIDYS study (i.e., the primary endpoint and endpoint used in the indirect treatment comparison) using RoB 2.

**Table 21: RoB 2 assessment for 4SC (primary) endpoint in EPIDYS**

| **EPIDYS (Study 48)** | | |
|---|---|---|
| **Study design** | | |
| ☑ | Individually-randomized parallel-group trial | |
| ☐ | Cluster-randomized parallel-group trial | |
| ☐ | Individually randomized cross-over (or other matched) trial | |
| **For the purposes of this assessment, the interventions being compared are defined as** | | |
| **Experimental:** | **Comparator:** | |
| Givinostat | ECM | |
| **Specify which outcome is being assessed for risk of bias** | | |
| 4SC | | |
| **Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed** | | |
| Geometric least squares mean ratios for the log transformed 4SC results at 18 months versus baseline of 1.27 (95% CI 1.17 to 1.37) in the givinostat group versus 1.48 (95% CI 1.32 to 1.66) in the placebo group (ratio 0.86; 95% CI 0.75 to 0.99, p=0.035 (Group A population) | | |
| **Is the review team's aim for this result…?** | | |
| ☑ | to assess the effect of assignment to intervention (the 'intention-to-treat' effect) | |
| ☐ | to assess the effect of adhering to intervention (the 'per-protocol' effect) | |
| **If the aim is to assess the effect of adhering to intervention, select the deviations from intended intervention that should be addressed (at least one must be checked):** | | |
| Not applicable | | |
| ☐ | occurrence of non-protocol interventions | |
| ☐ | failures in implementing the intervention that could have affected the outcome | |
| ☐ | non-adherence to their assigned intervention by trial participants | |
| **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)** | | |
| ☑ | Journal article(s) with results of the trial | |
| ☑ | Trial protocol | |
| ☑ | SAP | |
| ☐ | Non-commercial trial registry record (e.g. ClinicalTrials.gov record) | |
| ☐ | Company-owned trial registry record (e.g. GSK Clinical Study Register record) | |
| ☐ | "Grey literature" (e.g. unpublished thesis) | |
| ☐ | Conference abstract(s) about the trial | |
| ☑ | Regulatory document (e.g. Clinical Study Report, Drug Approval Package) | |
| ☐ | Research ethics application | |
| ☐ | Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research) | |
| ☐ | Personal communication with trialist | |
| ☑ | Personal communication with the sponsor | |
| **Risk of bias assessment** | | |
| Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used. | | |
| **Domain 1: Risk of bias arising from the randomization process** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | Yes. Randomisation was via interactive response technology (IRT). Eligible boys were randomised using a list generated by the statistician of the IRT provider (accessed by site staff telephoning the provider's system to receive a packaging number). Treatment was centrally assigned by an external organisation | Y |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | | Y |

| | | |
|---|---|---|
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | No. Baseline demographic and disease characteristics were similar in the givinostat and placebo groups | N |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias arising from the randomization process? | | NA |
| **Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | No. Boys, carers, investigators (including physiotherapists), and site and sponsor staff were masked to treatment assignment, with the placebo suspension indistinguishable in appearance and taste from givinostat | N |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | | N |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** | | NA |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** | | NA |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** | | NA |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | Yes, the study used an intention-to-treat analysis | Y |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | NA |
| **Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | No. Boys, carers, investigators (including physiotherapists), and site and sponsor staff were masked to treatment assignment, with the placebo suspension indistinguishable in appearance and taste from givinostat | N |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | | N |
| **2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?** | | NA |
| **2.4. [If applicable:] Were there failures in implementing the** | | NA |

| | | |
|---|---|---|
| **intervention that could have affected the outcome?** | | |
| **2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?** | No, mean compliance was greater than 98% in all groups | N |
| **2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | NA |
| **Domain 3: Missing outcome data** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | Yes, 95% of randomized participants completed the study and have data available for analysis | Y |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** | | NA |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** | | NA |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing outcome data? | | NA |
| **Domain 4: Risk of bias in measurement of the outcome** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | No, 4SC is a clinically meaningful, reliable and validated timed motor function test. 4SC was evaluated by trained physiotherapists masked to treatment and other assessments, with all baseline and 72-week visits recorded and reviewed by an expert, independent team of physiotherapists, not otherwise involved in the study, for quality assurance | N |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | No, see above | N |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | No, assessors were masked to treatment | N |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by** | | NA |

| | | |
|---|---|---|
| **knowledge of intervention received?** | | |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias in measurement of the outcome? | | NA |
| **Domain 5: Risk of bias in selection of the reported result** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | Yes, the SAP was finalised prior to study unblinding | Y |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...**<br>**5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | No, the numerical result being assessed was the time to climb 4 standard-sized stairs recorded in seconds evaluated by qualified functional evaluators (i.e., physiotherapists). The numerical result being assessed was the 4SC time at the end of the study compared with the 4SC time at baseline, in accordance with the study SAP and protocol | N |
| **5.3 ... multiple eligible analyses of the data?** | No, reported results for the outcome measurement correspond to the intended analyses | N |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | NA |
| **Overall risk of bias** | | |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the overall predicted direction of bias for this outcome? | | NA |

Abbreviations: 4SC, four-stair climb; ECM, established clinal management; N, no; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; SAP, Statistical analysis plan; Y, yes.

**Table 22: RoB 2 assessment for loss of ambulation endpoint (used in the ITC) in EPIDYS**

| | |
|---|---|
| **EPIDYS (Study 48)** | |
| **Study design** | |
| ☑ | Individually-randomized parallel-group trial |
| ☐ | Cluster-randomized parallel-group trial |
| ☐ | Individually randomized cross-over (or other matched) trial |
| **For the purposes of this assessment, the interventions being compared are defined as** | |
| **Experimental:** | **Comparator:** |
| Givinostat | ECM |
| **Specify which outcome is being assessed for risk of bias** | |
| Loss of ambulation | |
| **Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed** | |
| Proportion of patients who lost ambulation at 18 months compared with baseline: 0 patients in givinostat versus 1 patient in ECM group (odd ratio non calculable) | |
| **Is the review team's aim for this result…?** | |
| ☑ | to assess the effect of assignment to intervention (the 'intention-to-treat' effect) |
| ☐ | to assess the effect of adhering to intervention (the 'per-protocol' effect) |
| **If the aim is to assess the effect of adhering to intervention, select the deviations from intended intervention that should be addressed (at least one must be checked):** | |
| Not applicable | |
| ☐ | occurrence of non-protocol interventions |
| ☐ | failures in implementing the intervention that could have affected the outcome |
| ☐ | non-adherence to their assigned intervention by trial participants |
| **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)** | |
| ☑ | Journal article(s) with results of the trial |
| ☑ | Trial protocol |
| ☑ | SAP |
| ☐ | Non-commercial trial registry record (e.g. ClinicalTrials.gov record) |
| ☐ | Company-owned trial registry record (e.g. GSK Clinical Study Register record) |
| ☐ | "Grey literature" (e.g. unpublished thesis) |
| ☐ | Conference abstract(s) about the trial |
| ☑ | Regulatory document (e.g. Clinical Study Report, Drug Approval Package) |
| ☐ | Research ethics application |
| ☐ | Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research) |
| ☐ | Personal communication with trialist |
| ☑ | Personal communication with the sponsor |

| **Risk of bias assessment** | | |
|---|---|---|
| Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used. | | |
| **Domain 1: Risk of bias arising from the randomization process** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | Yes. Randomisation was via interactive response technology (IRT). Eligible boys were randomised using a list generated by the statistician of the IRT provider (accessed by site staff telephoning the provider's system to receive a packaging number). Treatment was centrally assigned by an external organisation | Y |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | | Y |

| | | |
|---|---|---|
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | No. Baseline demographic and disease characteristics were similar in the givinostat and placebo groups | N |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias arising from the randomization process? | | NA |
| **Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | No. Boys, carers, investigators (including physiotherapists), and site and sponsor staff were masked to treatment assignment, with the placebo suspension indistinguishable in appearance and taste from givinostat | N |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | | N |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** | | NA |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** | | NA |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** | | NA |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | Yes, the study used an intention-to-treat analysis | Y |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | NA |
| **Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | No. Boys, carers, investigators (including physiotherapists), and site and sponsor staff were masked to treatment assignment, with the placebo suspension indistinguishable in appearance and taste from givinostat | N |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | | N |
| **2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?** | | NA |
| **2.4. [If applicable:] Were there failures in implementing the** | | NA |

| | | |
|---|---|---|
| **intervention that could have affected the outcome?** | | |
| **2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?** | No, mean compliance was greater than 98% in all groups | N |
| **2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | NA |
| **Domain 3: Missing outcome data** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | Yes, 95% of randomized participants completed the study and have data available for analysis | Y |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** | | NA |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** | | NA |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing outcome data? | | NA |
| **Domain 4: Risk of bias in measurement of the outcome** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | No, loss of ambulation is a clinically meaningful, binary, objective outcome measure. It was clearly defined in the EPIDYS study as any patients who satisfied both of the following criteria: unable to perform the 6-minute walking test due to physical inability and unable to complete the 10-metre walk/run test in ≤30 seconds without any support or devices (10-metre walk/run test grading ≤2). It was evaluated by trained physiotherapists masked to treatment and other assessments | N |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | No, see above | N |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware** | No, assessors were masked to treatment | N |

| | | |
|---|---|---|
| **of the intervention received by study participants?** | | |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** | | NA |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias in measurement of the outcome? | | NA |
| **Domain 5: Risk of bias in selection of the reported result** | | |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | Yes, the SAP was finalised prior to study unblinding | Y |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...**<br>**5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | No, the numerical result being assessed was the proportion of subjects with loss of ambulation (defined in 4.1 above) at end of study compared with baseline, in accordance with the study SAP and protocol | N |
| **5.3 ... multiple eligible analyses of the data?** | No, reported results for the outcome measurement correspond to the intended analyses | N |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | NA |
| **Overall risk of bias** | | |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the overall predicted direction of bias for this outcome? | | NA |

Abbreviations: ECM, established clinal management; N, no; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; SAP, Statistical analysis plan; Y, yes.

## *Textual clarification*

**C7**. In Section B.3.3.1 when discussing analysis 2, did the company mean that transition probabilities are under-estimated, since the company argues that a 15.5 year age of loss of ambulation is too high?

**Response:** In Section B.3.3.1 of the CS, it is stated: "*The second analysis (updated NHM [analysis 2]) explored the potential for over-estimated transition probabilities in the published NHM earlier in the disease pathway.*" We would like to apologise for the error in this statement, the sentence should instead state: "*The second analysis (updated NHM [analysis 2]) explored the potential for under-estimated transition probabilities in the published NHM earlier in the disease pathway, which then results in an over-estimation of age at key milestones*." Thank you for bringing this to our attention.

**C8.** Please send a corrected version of this first paragraph of Section B.3.7 as the references are broken.

**Response:** Thank you for flagging. The correct referencing is included below.

**3.7 Benefits not captured in the QALY calculation**

As described in Section B.3.4.6, the givinostat CEM includes caregiver utilities for two caregivers, aligning with feedback in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135) [Reference 130 in the submission document B].[23] This likely underestimates the substantial caregiver and wider societal impact from givinostat for the treatment of DMD; assuming that a DMD diagnosis only effects two caregivers in a family is likely to substantially underestimate the potential burden of this debilitating disease. About one-third of parents believe that DMD has a negative influence on the psychological well-being and social life of the unaffected siblings [Reference 102 in the submission document B].[60] Siblings often run the risk of being "voiceless" and may feel invisible to parents focused on the complex needs of their child with DMD. [References 106 and 107 in the submission document B].[61,62] Grandparents and other informal caregivers are also negatively impacted due to the increased burden on the family, and an increased need for informal care for boys with DMD.

**C9. When do you anticipate UK MHRA marketing approval will be completed?**

**Response:** The MHRA granted approval for givinostat on 20 December 2024 (PLGB 13297/0017), for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older, via the International Recognition Procedure.[63]

Givinostat has not been studied in patients who commence treatment in the non-ambulatory phase. Therefore, a Conditional Marketing Authorisation (CMA) has been

stipulated for this population whilst awaiting confirmatory clinical trial results. The condition of the CMA is to perform further studies and/or to provide additional measures to minimise the risk in patients who are already non-ambulatory when the start givinostat treatment.

The only conditions stipulated in the MHRA CMA relate to patients who are starting givinostat when already non-ambulatory. The specific obligation as part of the givinostat CMA is the completion and submission to MHRA of: PIP MHRA-101094-23-M01 (Study DSC/14/2357/50; ULYSSES): A randomised, placebo-controlled study to evaluate the efficacy and safety of givinostat in paediatric non-ambulant patients. For further information please refer to the givinostat Public Assessment Report.[63]

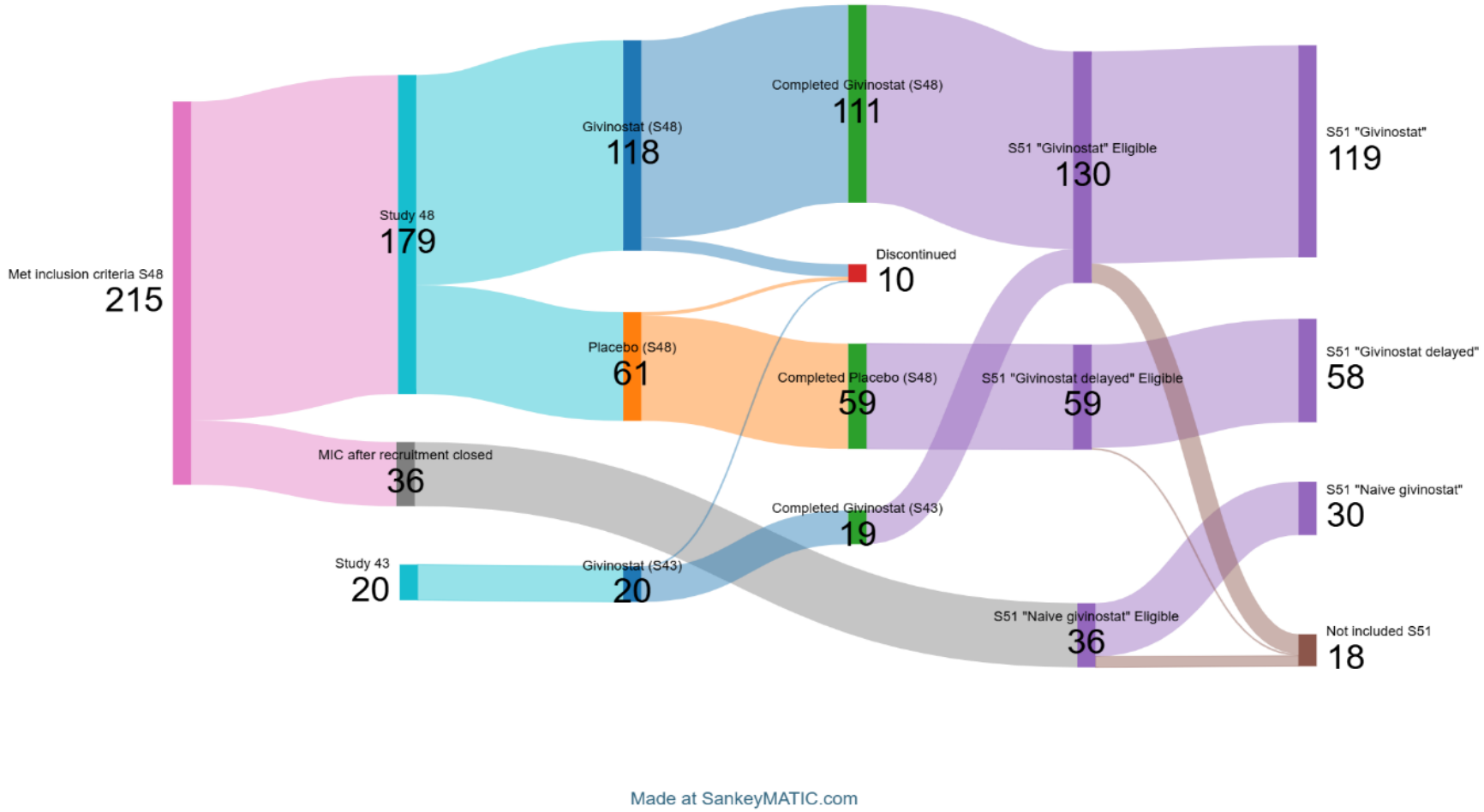
In summary, the population in scope for the current givinostat NICE submission (patients with DMD who start in the ambulant phase of disease, and boys with DMD who become non-ambulant over time while remaining on givinostat), is clearly distinct from the population related to the conditional approval (patients who are already non-ambulatory when the start givinostat treatment). Because of the MHRA single marketing authorisation for givinostat, it cannot have two different approval types for the sub-populations (ambulatory and non-ambulatory).

***Table 1: comparison of outcomes in NICE FINAL SCOPE and Company clinical SLR***

| NICE Scope | CS Clinical SLR |
|---|---|
| The outcome measures to be considered include:<br>• walking ability (ambulation)<br>• muscle function<br>• muscle strength<br>• ability to undertake activities of daily living<br>• bone function<br>• cardiac function<br>• concordance and optimisation of treatment<br>• endocrine function<br>• lung function<br>• time in wheelchair<br>• number of falls<br>• time to scoliosis<br>• lower body function<br>• upper body function<br>• mortality<br>• adverse effects of treatment<br>• • health-related quality of life (people with DMD and carers). | • Natural history data for disease course<br>• Efficacy (including but not limited to)<br>  ○ 4SC<br>  ○ Walking ability (ambulation), e.g. using the 6MWT or 10-meter walking test<br>  ○ TTR<br>  ○ Ambulation, e.g. using time to wheelchair, NSAA, or number of falls<br>  ○ Ventilation outcomes, including non-invasive night-time ventilation and full ventilation<br>  ○ Vastus lateralis fat fraction<br>  ○ Muscle strength, e.g. using hand-to-mouth function, knee flexion or extension, elbow flexion or extension<br>  ○ Cardiac function, e.g. using ECG or ECHO<br>  ○ Lung function, e.g. FVC<br>  ○ Time to scoliosis<br>• Safety<br>  ○ Mortality<br>  ○ Adverse effects of treatment<br>• PROs<br>  ○ Utility data<br>• Correlation between outcomes in ambulatory and non-ambulatory patients, meeting all three of the following criteria:<br>  ○ Compare at least two interventions (one can be placebo)<br>  ○ Have an “early” endpoint e.g. some in the ambulatory phase (could be walking endpoint, standing, climbing, and loss of ambulation) |

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| | ○ Have a “late” endpoint in the non-ambulatory phase e.g. loss of hand-to-mouth function, respiratory, cardiac, mortality<br>Utility data will be cross-checked in the identified studies in addition to the utility searches (Appendix H) |

***Enlarged Figure from question A7***



## Cost-effectiveness results

The base case ICER presented in the original CS is [redacted], including the proposed PAS for givinostat in the form of a simple discount of [redacted]%.

Three scenarios are presented in this response to the EAG's Clarification Questions: B8, B9, and B17. Table 23 outlines the incremental change from the original base-case ICER for each of the scenarios presented in this response, including:

- Additional monitoring costs for givinostat (see response to B8)
- Inclusion of costs related to tertiary care, medical aids, and investments (see response to B9)
- Differential health state costs and patient utilities for health state 8 vs. health state 7 (see response to B17)

**Table 23: Step change in base case ICER for each of the scenarios presented in this response**

| | ICER step change | % change each step |
|---|---|---|
| Original base case | [redacted] | NA |
| Additional monitoring costs for givinostat (B8) | [redacted] | 0.8% |
| Inclusion of costs related to tertiary care, medical aids, and investments (B9) | [redacted] | 2.5% |
| Differential health state costs and patient utilities for health state 8 vs. health state 7 (B17) | [redacted] | -1.5% |

Abbreviations: ICER, incremental cost-effectiveness ratio.

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

**Information on completing this submission**

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable

We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.

Your response should not be longer than 10 pages.

## About you

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| **1.Your name** | [redacted] |
| **2. Name of organisation** | Action Duchenne |
| **3. Job title or position** | [redacted] |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | Action Duchenne is a UK-based charitable organisation that focuses on supporting individuals and families affected by Duchenne muscular dystrophy (DMD). DMD is a genetic muscle-wasting condition that primarily affects boys and young men. The organisation is dedicated to improving the lives of those with DMD through research, advocacy, education and support. Action Duchenne is funded by donations, community fundraisers, grants, and sponsorships from pharmaceutical companies.<br>Number of staff: twelve.<br>More information can be found here: https://www.actionduchenne.org/about-us/what-we-do/. Registered Charity No: 1101971 |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]**<br>**If so, please state the name of the company,** | £15,000 sponsorship funding received from ITF Pharma UK (Italfarmaco Group) towards 2024 Action Duchenne's International Conference.<br>The funding is not ongoing.<br>The purpose of funding is not related to Givinostat for treating symptoms associated with Duchenne muscular dystrophy [ID6323].<br>With the support from our sponsors and exhibitors, the charity is able to offer free conference tickets to all UK and international Duchenne families. |

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| **amount, and purpose of funding.** | |
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | Working alongside patient expert groups such as Muscular Dystrophy UK and Duchenne UK, we have access to information gatherer via the following methods:<br>● One-to-one discussion with patients/ carers & parents.<br>● Regular focus and support group meetings for Patients and Carers.<br>● Science education programmes and International conference feedback.<br>● Project HERCULES, a Duchenne UK-led international collaboration to develop evidence and tools to support HTA for new products for DMD. |

**Living with the condition**

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| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | Duchenne muscular dystrophy (DMD) is a genetically inherited muscle disorder resulting from mutations in the dystrophin gene located on the X chromosome. This X-linked recessive disorder is characterised by progressive skeletal muscle degeneration, predominantly affecting males. In the United Kingdom, DMD has an estimated incidence of one in 3,500-6000 male births, with approximately 2500 people in the UK currently diagnosed with DMD. Typically, the initial symptoms of DMD manifest between the ages of one and three years.<br><br>The progressive nature of DMD presents a significant burden on caregivers. The emotional toll of diagnosis is often compounded by the lack of readily available psychological support. As the disease progresses, the increasing need for physical assistance can lead to caregiver burnout and require significant adjustments to work schedules and personal lives and relationships. This burden is further amplified by the potential for DMD to affect multiple children within a family, creating a complex and emotionally demanding caregiving environment. Furthermore, the absence of a newborn screening program or national screening program for young children in the United Kingdom can contribute to delayed diagnosis of DMD. This delay can have a significant negative impact not only on the course of patient care but also on families, particularly those who may have multiple children affected by DMD by the time the eldest child receives a diagnosis.<br><br>While DMD primarily manifests in males, female carriers of the mutated dystrophin gene can experience significant psychological distress. The knowledge of carrying a genetic condition with potentially devastating consequences for future offspring can cause anxiety and fear. Additionally, the possibility of having multiple children affected by DMD before diagnosis can create a sense of helplessness and guilt. Furthermore, female carriers may face complex family dynamics and emotional strain as they navigate reproductive choices and grapple with the emotional toll of supporting loved ones living with DMD.<br><br>There have been a range of estimates of life expectancy and Project HERCULES commissioned a systematic review of available data to better understand life expectancy. This found median life expectancy was 22.0 years (95% CI 21.2, 22.4), with patients born after 1990 having a median life expectancy of 28.1 years (95% CI 25.1, 30.3)[1]. A further study in 2023 estimated that patients spend approximately 9.5 years in ambulatory states, 1.5 years in the transfer state, and the remainder of their lives in non-ambulatory states, with a median predicted survival of 29.8 years (95% CI: 29.1, 30.8).[2]<br><br>Life expectancy has increased through improvements in the standards of care, not treatments, but it is worth noting many patients still die before they reach their twenties. In June 2017 an eleven-year-old with DMD from Warrington passed away. (See https://www.warringtonguardian.co.uk/news/15389094.warrington-wolves-to- |

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| | remember-joshua-morris-on-day-he-would-have-been-mascot-for-12th-birthday/) And in 2022 a sixteen-year-old from Dublin with DMD passed away. (See: https://www.mirror.co.uk/news/uk-news/parents-boy-16-who-died-27433996).<br><br>Standard medical management of DMD requires consideration of the use of corticosteroids as well as respiratory, cardiac, orthopaedic, psychosocial, endocrinology, nutrition/gastrointestinal and rehabilitative interventions. The potential for corticosteroids was published in 1989 in a randomised, double blind study of over 100 patients. Corticosteroids slow the progression of muscle weakness and delay some of the complications of the disease, but they do not treat or correct the underlying causes of DMD. |

[1] Life Expectancy in Duchenne Muscular Dystrophy Reproduced Individual Patient Data Meta-analysis, Broomfield et al, Neurology Dec 2021, https://n.neurology.org/content/97/23/e2304

[2] Developing a Natural History Model for Duchenne Muscular Dystrophy, Broomfield et al, Jan 2023, PREPRINT (Version 1) available at Research Square https://www.researchsquare.com/article/rs-2405860/v1

## Current treatment of the condition in the NHS

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| **7. What do patients or carers think of current treatments and care available on the NHS?** | The main pharmaceutical intervention and comparator are corticosteroids, which are prescribed off label. Corticosteroids (prednisone and deflazacort) should be considered for all patients with DMD, according to the care recommendations published in the Lancet[3]. Corticosteroids have several side effects that have the potential to impact quality of life such as bone weakening and adrenal crisis.<br>These side effects can potentially create a cost:benefit balance that often causes anxiety around long term use. Therefore, there is an urgent and unmet need for additional treatments that work alongside current treatments, or as an alternative, that either addresses the costs (side effects) and/or improves the benefit (improved delay of disease progression).<br><br>Parent/carer testimonies on currently available NHS treatments and care:<br><br>*"I am worried if/when I do start the medication for my son what the side effects would be like, as it will be hard for me to manage".*<br>- Parent/Carer of Boy with DMD<br><br>*"There is definitely not enough [treatment support or expertise], and there seems to be limited understanding of DMD in relation to both steroids and the condition as a whole".*<br>- Parent/Carer of Boy with DMD |
| **8. Is there an unmet need for patients with this condition?** | Yes. Corticosteroids (prednisone or deflazacort) are the only treatment available to patients in the UK that isn't mutation specific, but they are associated with numerous side effects. This means there is a greatly unmet need for an increase in the number of treatments available for DMD patients, that can act alongside current treatments or as an alternative, with the aim of improving the delay of disease progression and/or improving the standards of care received by patients. |

[3] Diagnosis and management of Duchenne muscular dystrophy, part 1, Birnkrant et al, Lancet Neurology, Mar 2018, https://pubmed.ncbi.nlm.nih.gov/29395989/

## Advantages of the technology

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| **9. What do patients or carers think are the advantages of the technology?** | The major advantage of this technology/ treatment is its broad applicability. Given the treatment is an epigenetics treatment, it is not directed at individuals with a certain dystrophin gene mutation type, as seen with some potential gene therapies. The treatment has been tested alongside current corticosteroid regimens with positive results, meaning the number of patients that would have access, if approved, would be large with fewer exclusion criteria.<br><br>Parent/carer testimony on experiences with Givinostat:<br><br>In response to the question 'Do you feel the Givinostat treatment led to a delay in disease progression (such as loss of ambulation) compared to initial diagnosis expectations?'<br><br>"*Yes, my son is still walking at 17 and still fairly active. I think this is due to being on Givinostat. I was told he probably wouldn't walk by early teens when he was diagnosed when he was 5"*<br>- Parent/carer of Son with DMD using Givinostat<br><br>In response to the question 'How did the treatment impact your, or the person you care for, overall quality of life?'<br><br>*"The treatment has improved my sons quality of life being still mobile at 17 and only using his wheelchair part time. We are so grateful we got to take part in the trial and are so happy this treatment could be available to all."*<br>- Parent/carer of Son with DMD using Givinostat |

## Disadvantages of the technology

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| **10. What do patients or carers think are the disadvantages of the technology?** | We have received no patient/carer testimony on the disadvantages of this treatment. |

## Patient population

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| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | Givinostat is an epigenetic treatment. This means that the mutation type of DMD is irrelevant and the treatment can be used by most patients. We are not aware of any factors benefiting groups of patients more or less. |

## Equality

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| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | We are not aware of any equality issues with this technology in relation to DMD. |

## Other issues

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| **13. Are there any other issues that you would like the committee to consider?** | No |

## Key messages

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| **14. In up to 5 bullet points, please summarise the key messages of your submission.** | 1) Treatments available for DMD are limited. Additional treatments supported by clinical experts would greatly improve patient standards of care through improving symptom management.<br><br>2) Families and patients living with DMD, greatly emphasise the need for more treatments to be available that offer the chance of improving the delay of disease progression. We believe the clinical data suggests Givinostat may address this need.<br><br>3) Givinostat is a treatment targeted at usage in conjunction with corticosteroid use. This gives opportunity to use the treatment in combination and possible synergy with currently approved conventional treatments.<br><br>4) Givinostat is an epigenetic non-mutation specific treatment. This makes the treatment broadly applicable to patients with different site mutations in the dystrophin gene.<br><br>5) Most emerging therapies are focused on fixing the underlying genetic cause of DMD; through either gene therapy or gene editing, to produce a microdystrophin as a replacement for the mutated dystrophin protein in DMD. Therefore, there is an unmet need for muscle-repairing therapies, such as Givinostat, which target the inflammatory causes of the disease. |

Thank you for your time.

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal
# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]
# Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

## About you

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| **1.Your name** | [redacted] |
| **2. Name of organisation** | Duchenne UK<br><br>[Please note this is a joint submission with Muscular Dystrophy UK] |
| **3. Job title or position** | [redacted] |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | Duchenne UK is a patient-led medical research charity focused on Duchenne muscular dystrophy. More information can be found here: https://www.duchenneuk.org Registered Charity No. 1147094.<br><br>Muscular Dystrophy UK (MDUK) is the charity bringing individuals, families and professionals together to beat muscle wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 110,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them.<br>More information can be found at https://www.musculardystrophyuk.org/ Registered Charity No. 205395. Scottish Registered Charity No. SC039445 |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]** | Duchenne UK has received funding from Italfarmaco in the last 12 months.<br><br>Italfarmaco were one of the organisations which co-sponsored Duchenne UK's New Horizon conference in 2024. They contributed £10,000 in Dec 2023.<br><br>Italfarmaco are one of 13 pharmaceutical companies which have co-sponsored Project HERCULES since 2018. Italfarmaco have made one payment towards Project HERCULES, of £120,000 in Feb 2024.<br><br>Muscular Dystrophy UK have received the following:<br><br>**ITF Pharma Ltd** |

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| **If so, please state the name of the company, amount, and purpose of funding.** | £3,750 + VAT for Bronze sponsorship - UK Neuromuscular Translational Research Conference 2024, March 2024<br><br>**PTC Therapeutics**<br>£16K + VAT as series sponsor for MDUK's Virtual Seminar Series, August 2024 |
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No. |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | • A survey of 200 people personally affected by DMD conducted in April 2024.<br>• Input from families who are taking part in the givinostat trial gathered in June/July 2024.<br>• Project HERCULES, a Duchenne UK-led international collaboration to develop evidence and tools to support HTA for new products for DMD. In particular:<br>  ○ Life Expectancy in Duchenne Muscular Dystrophy Reproduced Individual Patient Data Meta-analysis, Broomfield et al, Neurology Dec 2021, https://n.neurology.org/content/97/23/e2304<br>  ○ The burden of long-term corticosteroid use in the treatment of Duchenne Muscular Dystrophy in the UK, Tolley et al, Value in Health, December 2022, https://www.valueinhealthjournal.com/article/S1098-3015(22)04283-8/fulltext<br>  ○ Developing a Natural History Model for Duchenne Muscular Dystrophy, Broomfield et al, November 2023, https://link.springer.com/article/10.1007/s41669-023-00450-x |

**Living with the condition**

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| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene. This gene is an x-linked genetic disorder characterized by the progressive skeletal muscle degeneration, primarily in boys. It affects one out of 3,500-6,000[1] live male births in the UK. Patients generally exhibit symptoms between one and three years of age.<br><br>There is no newborn screening programme or national screening programme for young children in the UK, and this can lead to delayed diagnosis. In addition to the impact on patient care, this can have a huge impact on families who may have two or more children with DMD by the time of diagnosis of the oldest child.<br><br>The diagnosis of DMD is devastating for a family and there is often very little psychological support for them to come to terms with it. Caregivers – often both parents – can suffer with depression and anxiety after diagnosis and have prolonged absences from work. Because of the progressive nature of the disease, the demands and impact on the caregiver increases as patients lose muscle function and the ability to walk, and later on the use of their arms.<br><br>The primary symptoms of DMD are caused by a lack of dystrophin in the muscle. Children with DMD lose the ability to walk independently and most become reliant on wheelchairs for mobility between the ages of 8 and 13. Some children with DMD never walk. Many boys may initially retain the ability to weight bear and support transfers, for example from wheelchair to toilet or car, before losing the ability to stand. As DMD progresses patients will lose strength and mobility in their arms. They will lose the ability to feed themselves, brush their teeth or undertake any self-care activities. Patients are likely to retain some function in the hands and fingers into adult life.<br><br>Most individuals with DMD experience serious respiratory, orthopaedic, and cardiac complications. By the age of 18, the majority of patients require ventilation support at night. Respiratory complications and cardiomyopathy are common causes of death. Dystrophin is also present in the brain and many people with DMD have learning disabilities or neurological disorders such as autism, possibly due to the lack of brain dystrophin. These usually remain static and do not worsen as DMD progresses, however they can add a significant burden on care and educational provision due to the more complex needs of young people with DMD who also present with neurobehavioural comorbidities.<br><br>There have been a range of estimates of life expectancy and Project HERCULES commissioned a systematic review of available data to better understand life expectancy. This found median life expectancy was 22.0 years (95% CI 21.2, 22.4), with patients born after 1990 having a median life expectancy of 28.1 years (95% CI 25.1, |

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| | 30.3)[2]. A further study in 2023 estimated that patients spend approximately 9.5 years in ambulatory states, 1.5 years in the transfer state, and the remainder of their lives in non-ambulatory states, with a median predicted survival of 29.8 years (95% CI: 29.1, 30.8).[3]<br><br>Life expectancy has increased through improvements in the standards of care, and treatment of the symptoms of DMD such as with corticosteroids, but it is worth noting many patients still die before they reach their twenties. In June 2017 an eleven-year-old with DMD from Warrington passed away. (See https://www.warringtonguardian.co.uk/news/15389094.warrington-wolves-to-remember-joshua-morris-on-day-he-would-have-been-mascot-for-12th-birthday/ ) And in 2022 a sixteen-year-old from Dublin with DMD passed away. (See: https://www.mirror.co.uk/news/uk-news/parents-boy-16-who-died-27433996 )<br><br>Standard medical management of DMD requires consideration of the use of corticosteroids as well as respiratory, orthopaedic, and rehabilitative interventions, in addition to preventative measures of cardiac complication, such as the use of ACE inhibitors. Corticosteroids slow the progression of muscle weakness and delay some of the complications of the disease, but they do not treat or correct the underlying causes of DMD. Steroids also have severe and detrimental side effects that can significantly impact on quality of life. Experiences of these side effects include:<br><br>1. serious effects on bone health leading to excess fractures which can cause pain and speed up the loss of muscle function<br>2. weight gain, extreme in some patients<br>3. adrenal insufficiency and crisis (which can be lethal, if not administered correctly)<br>4. stunted growth, which causes psychological pain<br>5. delayed puberty and associated psychological challenges behavioural problems. |

[1]Natural history of Duchenne muscular dystrophy in the United Kingdom: A descriptive study using the Clinical Practice Research Datalink, Broomfield et al, Brain and Behavior, Nov 2023 https://onlinelibrary.wiley.com/doi/full/10.1002/brb3.3331

[2]Life Expectancy in Duchenne Muscular Dystrophy Reproduced Individual Patient Data Meta-analysis, Broomfield et al, Neurology Dec 2021, https://n.neurology.org/content/97/23/e2304

[3] Developing a Natural History Model for Duchenne Muscular Dystrophy, Broomfield et al, Nov 2023, https://link.springer.com/article/10.1007/s41669-023-00450-x

**Current treatment of the condition in the NHS**

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| **7. What do patients or carers think of current treatments and care available on the NHS?** | The main pharmaceutical intervention and comparator are corticosteroids, which are prescribed off label. Corticosteroids (prednisone and deflazacort) should be considered for all patients with DMD, according to the care recommendations published in the Lancet[4]. Corticosteroids have significant side-effects as outlined in section 6. While givinostat is not intended to replace corticosteroids entirely, it is plausible that it could reduce the reliance on them – and in turn reduce the incidence of side-effects.<br><br>There is an urgent need for new treatments for DMD. When asked in April 2024 whether they thought there should be more treatment options for DMD, not one parent/patient respondent replied 'no'.<br><br>While the UK is lucky to have several neuromuscular specialists who are expert in the field of DMD, knowledge outside of specialist clinics among healthcare professionals can be low. Less than a third or respondents reported that those working in the healthcare system have a 'good' or 'very good' understanding and awareness of DMD. More than a quarter answered 'bad' or 'very bad' to this question.<br><br>Respondents to the April 2024 survey spoke of their dismay at the lack of treatments, and the harsh side effects of medicines like steroids.<br><br>*"There aren't any effective treatments for Duchenne that we can access. Steroids are helping to a degree but having multiple side effects eg weight gain, osteoporosis, cataracts. My son has been hospitalised with vertebral fractures as a consequence of steroid use."* -Parent/carer to a boy between 12 and 16 years of age with DMD.<br><br>*"Not great, the steroids have really impacted on our son weight, even with watching what he eats. But they have kept him mobile till 10, he's just about to go permanently into his electric wheelchair."* -Parent/carer to a boy between 9 and 12 years of age with DMD.<br><br>*"I would love more options and regularly monitor the pharmaceutical landscape. If I had one wish in the world it would be for more treatment options."* -Parent/carer to a boy between 5 and 8 years of age with DMD. |
| **8. Is there an unmet need for patients with this condition?** | Yes. There is only one approved treatment for DMD in the UK (ataluren/Translarna) but this has recently received a non-renewal of authorisation in the EMA due to concerns over its efficacy, and it is currently under review by the MHRA.<br><br>In addition, ataluren is only suitable for those patients with a nonsense mutation (which is approximately 10% of the DMD population). |

[4] Diagnosis and management of Duchenne muscular dystrophy, part 1, Birnkrant et al, Lancet Neurology, Mar 2018, https://pubmed.ncbi.nlm.nih.gov/29395989/

## Advantages of the technology

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| **9. What do patients or carers think are the advantages of the technology?** | We believe the best way to assess the advantages of a treatment is through a rigorous clinical trial process. However, we have also collected anecdotal data for the committee. While we trust the committee will judge givinostat by the results of clinical trial data, we hope these anecdotes will provide an insight into the people behind the numbers too.<br><br>Families of patients who have received givinostat are positive about the treatment, and attribute many advantages to it. These advantages stem from retained limb function, which can prolong ambulation and increase independence. Maintaining this independence and not needing support from a parent or carer to, for example, use the toilet or dress oneself, is hugely advantageous at any age, but it should be noted that the average age of loss of ambulation is ~14 years, after spending on average 1.5 years in the transfer stage[5]. The teenage years are the most formative in any person's life, and the advantages of pushing the age of loss of ambulation any year beyond 14, or increasing the amount of time spent in the ambulatory or transfer stages, cannot be overstated.<br><br>As an example, one family reported that their 18-year-old son was still ambulatory, and did not need to use an expensive powered wheelchair (most will require one by age 14). Their son occasionally used a vastly cheaper manual wheelchair, which had another benefit – it required upper limb function to use, which contributed to their mental and physical health (expanded on in the paragraph below). The family reported that the 18-year-old could drive an un-adapted car, avoiding requiring a costly adapted vehicle, and could wash and dress themselves. The fact that someone with DMD – the most severe form of muscular dystrophy – could drive a car is remarkable, and should not be glossed over. This family's experience represents a huge increase in quality of life for not just the person with DMD, who can enjoy a longer and more active life through their important teenage years, but also for their family, who otherwise would be performing onerous caring duties.<br><br>Retaining mobility, even if the decline still progresses, creates additional benefits. Families reported that they felt that physically, heart and lung function remained healthier than they otherwise would have if their son was non-ambulant, due to exercise. Mental health should not be ignored, and while it is much harder to record, mental health benefits from retained ambulation. Feeling as though the progression of the disease has slowed can be hugely beneficial to wellbeing and contributes to a positive outlook - not only to the person with DMD but their family too – in addition to the advantages of retaining independence outlined above.<br><br>There is a very strong desire for an approval of givinostat within the entire DMD community – within both ambulant and non-ambulant groups.<br><br>This is based on three factors: |

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| | • The results of the Phase 3 EPIDYS study<br>EPIDYS demonstrated that givinostat is slowing down the progression. Results from the Italfarmaco Pivotal Phase 3 EPIDYS Study of givinostat in DMD were published in The Lancet Neurology in March 2024. The EPIDYS clinical trial met its primary endpoint: change in four-stair climb assessment from baseline to 72 weeks, which demonstrated the potential of givinostat to delay disease progression when added to corticosteroid treatment. givinostat-treated boys also showed favourable outcomes on key secondary endpoints assessed in the study.<br><br>"The trial results look promising: although this is not a cure it looks to slow down disease progression. If it can keep my son walking for longer, and enable him to climb stairs for longer, which means he can go to friends' houses or granny's for dinner, that will have a hugely beneficial effect on his life and on ours as his parent carers". -Parent of a 16-year old boy with DMD<br><br>• The personal experience of givinostat among the DMD community<br>People with DMD and parents of people with DMD share their experience of DMD and compare the progression of the disease between those who have been able to take part in a trial and those who haven't. Parents whose sons are on the trial are sharing the positive impact of being in the trial which adds to the popular perception that givinostat is, while not a cure for DMD, is slowing down its progression.<br><br>• The lack of current treatments for DMD<br>In April 2024, a survey of the DMD community undertaken by Duchenne UK, asked whether they thought there should be more treatment options for DMD, not one parent/patient respondent replied 'no'. When asked 'How do you feel about the current treatment options for DMD?', givinostat and its approval was referenced:<br><br>"I feel they are extremely limited. I really hope that givinostat gets approved in the UK very quickly." |

[5] Developing a Natural History Model for Duchenne Muscular Dystrophy, Broomfield et al, Nov 2023, https://link.springer.com/article/10.1007/s41669-023-00450-x

## Disadvantages of the technology

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| **10. What do patients or carers think are the disadvantages of the technology?** | Together with Muscular Dystrophy UK, we believe that the benefit risk profile favours benefit with givinostat. Families of patients who have received givinostat suggested that there were no serious adverse events and that side effects were well tolerated. The drug, taken orally, has a horrible taste. Some had diarrhoea and one reported to us that their son was monitored for temporary decreased platelet count. As a result of still walking in their late teens, one family reported lower back pain from pressure applied to the spine from poor posture – though they also noted lower back pain was vastly more preferable than the alternative of losing ambulation. |

## Patient population

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| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | From our understanding, givinostat will benefit any patient, and is not specific to a certain mutation. |

## Equality

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| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | Many DMD patients have significant mobility issues. This should be taken into account, so no patients are denied access to a treatment because of travel requirements.<br>We are not aware of any other potential equality issues that should be taken into account, beyond those which should be considered for rare diseases in general. |

## Other issues

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| **13. Are there any other issues that you would like the committee to consider?** | No. |

## Key messages

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| **14. In up to 5 bullet points, please summarise the key messages of your submission.** | • DMD is a devastating condition, with no cure. There is a strong unmet need for effective treatments for DMD<br>• The standard medical management of DMD, corticosteroids, is accompanied with severe negative side effects<br>• Slowing the progression of the disease, producing incremental improvements, and retaining ambulation and upper limb function, would deliver large quality of life benefits to patients and their caregivers, and is highly desirable to patients and their carers<br>• There is a strong desire to access givinostat throughout the DMD community |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

## Your privacy

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NICE National Institute for Health and Care Excellence

- Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

## Patient Organisation Submission

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- Your response should not be longer than 10 pages.

## About you

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|---|---|
| **1.Your name** | [redacted] |
| **2. Name of organisation** | Muscular Dystrophy UK<br><br>Note that we are submitting the same response as Duchenne UK. |
| **3. Job title or position** | [redacted] |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | Muscular Dystrophy UK (MDUK) is the charity bringing individuals, families and professionals together to beat muscle wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 110,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them.<br>More information can be found at https://www.musculardystrophyuk.org/ Registered Charity No. 205395. Scottish Registered Charity No. SC039445 |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]**<br>**If so, please state the name of the company,** | **ITF Pharma Ltd**<br>£3,750 + VAT for Bronze sponsorship - UK Neuromuscular Translational Research Conference 2024, March 2024<br><br>**PTC Therapeutics**<br>£16K + VAT as series sponsor for MDUK's Virtual Seminar Series, August 2024 |

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| **amount, and purpose of funding.** | |
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | • A survey of 200 people personally affected by DMD conducted in April 2024.<br>• Input from families who are taking part in the givinostat trial gathered in June/July 2024.<br>• Project HERCULES, a Duchenne UK-led international collaboration to develop evidence and tools to support HTA for new products for DMD. In particular:<br>  ○ Life Expectancy in Duchenne Muscular Dystrophy Reproduced Individual Patient Data Meta-analysis, Broomfield et al, Neurology Dec 2021, https://n.neurology.org/content/97/23/e2304<br>  ○ The burden of long-term corticosteroid use in the treatment of Duchenne Muscular Dystrophy in the UK, Tolley et al, Value in Health, December 2022, https://www.valueinhealthjournal.com/article/S1098-3015(22)04283-8/fulltext<br>Developing a Natural History Model for Duchenne Muscular Dystrophy, Broomfield et al, November 2023, https://link.springer.com/article/10.1007/s41669-023-00450-x |

**Living with the condition**

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| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene. This gene is an x-linked genetic disorder characterized by the progressive skeletal muscle degeneration, primarily in boys. It affects one out of 3,500-6,000[1] live male births in the UK. Patients generally exhibit symptoms between one and three years of age.<br><br>There is no newborn screening programme or national screening programme for young children in the UK, and this can lead to delayed diagnosis. In addition to the impact on patient care, this can have a huge impact on families who may have two or more children with DMD by the time of diagnosis of the oldest child.<br><br>The diagnosis of DMD is devastating for a family and there is often very little psychological support for them to come to terms with it. Caregivers – often both parents – can suffer with depression and anxiety after diagnosis and have prolonged absences from work. Because of the progressive nature of the disease, the demands and impact on the caregiver increases as patients lose muscle function and the ability to walk, and later on the use of their arms.<br><br>The primary symptoms of DMD are caused by a lack of dystrophin in the muscle. Children with DMD lose the ability to walk independently and most become reliant on wheelchairs for mobility between the ages of 8 and 13. Some children with DMD never walk. Many boys may initially retain the ability to weight bear and support transfers, for example from wheelchair to toilet or car, before losing the ability to stand. As DMD progresses patients will lose strength and mobility in their arms. They will lose the ability to feed themselves, brush their teeth or undertake any self-care activities. Patients are likely to retain some function in the hands and fingers into adult life.<br><br>Most individuals with DMD experience serious respiratory, orthopaedic, and cardiac complications. By the age of 18, the majority of patients require ventilation support at night. Respiratory complications and cardiomyopathy are common causes of death. Dystrophin is also present in the brain and many people with DMD have learning disabilities or neurological disorders such as autism, possibly due to the lack of brain dystrophin. These usually remain static and do not worsen as DMD progresses, however they can add a significant burden on care and educational provision due to the more complex needs of young people with DMD who also present with neurobehavioural comorbidities.<br><br>There have been a range of estimates of life expectancy and Project HERCULES commissioned a systematic review of available data to better understand life expectancy. This found median life expectancy was 22.0 years (95% CI 21.2, 22.4), with patients born after 1990 having a median life expectancy of 28.1 years (95% CI 25.1, |

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| | 30.3)[2]. A further study in 2023 estimated that patients spend approximately 9.5 years in ambulatory states, 1.5 years in the transfer state, and the remainder of their lives in non-ambulatory states, with a median predicted survival of 29.8 years (95% CI: 29.1, 30.8).[3]<br><br>Life expectancy has increased through improvements in the standards of care, and treatment of the symptoms of DMD such as with corticosteroids, but it is worth noting many patients still die before they reach their twenties. In June 2017 an eleven-year-old with DMD from Warrington passed away. (See https://www.warringtonguardian.co.uk/news/15389094.warrington-wolves-to-remember-joshua-morris-on-day-he-would-have-been-mascot-for-12th-birthday/ ) And in 2022 a sixteen-year-old from Dublin with DMD passed away. (See: https://www.mirror.co.uk/news/uk-news/parents-boy-16-who-died-27433996 )<br><br>Standard medical management of DMD requires consideration of the use of corticosteroids as well as respiratory, orthopaedic, and rehabilitative interventions, in addition to preventative measures of cardiac complication, such as the use of ACE inhibitors. Corticosteroids slow the progression of muscle weakness and delay some of the complications of the disease, but they do not treat or correct the underlying causes of DMD. Steroids also have severe and detrimental side effects that can significantly impact on quality of life. Experiences of these side effects include:<br><br>1. serious effects on bone health leading to excess fractures which can cause pain and speed up the loss of muscle function<br>2. weight gain, extreme in some patients<br>3. adrenal insufficiency and crisis (which can be lethal, if not administered correctly)<br>4. stunted growth, which causes psychological pain<br>delayed puberty and associated psychological challenges behavioural problems. |

[1]Natural history of Duchenne muscular dystrophy in the United Kingdom: A descriptive study using the Clinical Practice Research Datalink, Broomfield et al, Brain and Behavior, Nov 2023 https://onlinelibrary.wiley.com/doi/full/10.1002/brb3.3331

[2]Life Expectancy in Duchenne Muscular Dystrophy Reproduced Individual Patient Data Meta-analysis, Broomfield et al, Neurology Dec 2021, https://n.neurology.org/content/97/23/e2304

[3] Developing a Natural History Model for Duchenne Muscular Dystrophy, Broomfield et al, Nov 2023, https://link.springer.com/article/10.1007/s41669-023-00450-x

**Current treatment of the condition in the NHS**

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| **7. What do patients or carers think of current treatments and care available on the NHS?** | The main pharmaceutical intervention and comparator are corticosteroids, which are prescribed off label. Corticosteroids (prednisone and deflazacort) should be considered for all patients with DMD, according to the care recommendations published in the Lancet[4]. Corticosteroids have significant side-effects as outlined in section 6. While givinostat is not intended to replace corticosteroids entirely, it is plausible that it could reduce the reliance on them – and in turn reduce the incidence of side-effects.<br><br>There is an urgent need for new treatments for DMD. When asked in April 2024 whether they thought there should be more treatment options for DMD, not one parent/patient respondent replied 'no'.<br><br>While the UK is lucky to have several neuromuscular specialists who are expert in the field of DMD, knowledge outside of specialist clinics among healthcare professionals can be low. Less than a third or respondents reported that those working in the healthcare system have a 'good' or 'very good' understanding and awareness of DMD. More than a quarter answered 'bad' or 'very bad' to this question.<br><br>Respondents to the April 2024 survey spoke of their dismay at the lack of treatments, and the harsh side effects of medicines like steroids.<br><br>*"There aren't any effective treatments for Duchenne that we can access. Steroids are helping to a degree but having multiple side effects eg weight gain, osteoporosis, cataracts. My son has been hospitalised with vertebral fractures as a consequence of steroid use."* -Parent/carer to a boy between 12 and 16 years of age with DMD.<br><br>*"Not great, the steroids have really impacted on our son weight, even with watching what he eats. But they have kept him mobile till 10, he's just about to go permanently into his electric wheelchair."* -Parent/carer to a boy between 9 and 12 years of age with DMD.<br><br>*"I would love more options and regularly monitor the pharmaceutical landscape. If I had one wish in the world it would be for more treatment options."* -Parent/carer to a boy between 5 and 8 years of age with DMD. |
| **8. Is there an unmet need for patients with this condition?** | Yes. There is only one approved treatment for DMD in the UK (ataluren/Translarna) but this has recently received a non-renewal of authorisation in the EMA due to concerns over its efficacy, and it is currently under review by the MHRA.<br><br>In addition, ataluren is only suitable for those patients with a nonsense mutation (which is approximately 10% of the DMD population). |

[4] Diagnosis and management of Duchenne muscular dystrophy, part 1, Birnkrant et al, Lancet Neurology, Mar 2018, https://pubmed.ncbi.nlm.nih.gov/29395989/

## Advantages of the technology

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| **9. What do patients or carers think are the advantages of the technology?** | We believe the best way to assess the advantages of a treatment is through a rigorous clinical trial process. However, we have also collected anecdotal data for the committee. While we trust the committee will judge givinostat by the results of clinical trial data, we hope these anecdotes will provide an insight into the people behind the numbers too.<br><br>Families of patients who have received givinostat are positive about the treatment, and attribute many advantages to it. These advantages stem from retained limb function, which can prolong ambulation and increase independence. Maintaining this independence and not needing support from a parent or carer to, for example, use the toilet or dress oneself, is hugely advantageous at any age, but it should be noted that the average age of loss of ambulation is ~14 years, after spending on average 1.5 years in the transfer stage[5]. The teenage years are the most formative in any person's life, and the advantages of pushing the age of loss of ambulation any year beyond 14, or increasing the amount of time spent in the ambulatory or transfer stages, cannot be overstated.<br><br>As an example, one family reported that their 18-year-old son was still ambulatory, and did not need to use an expensive powered wheelchair (most will require one by age 14). Their son occasionally used a vastly cheaper manual wheelchair, which had another benefit – it required upper limb function to use, which contributed to their mental and physical health (expanded on in the paragraph below). The family reported that the 18-year-old could drive an un-adapted car, avoiding requiring a costly adapted vehicle, and could wash and dress themselves. The fact that someone with DMD – the most severe form of muscular dystrophy – could drive a car is remarkable, and should not be glossed over. This family's experience represents a huge increase in quality of life for not just the person with DMD, who can enjoy a longer and more active life through their important teenage years, but also for their family, who otherwise would be performing onerous caring duties.<br><br>Retaining mobility, even if the decline still progresses, creates additional benefits. Families reported that they felt that physically, heart and lung function remained healthier than they otherwise would have if their son was non-ambulant, due to exercise. Mental health should not be ignored, and while it is much harder to record, mental health benefits from retained ambulation. Feeling as though the progression of the disease has slowed can be hugely beneficial to wellbeing and contributes to a positive outlook - not only to the person with DMD but their family too – in addition to the advantages of retaining independence outlined above.<br><br>There is a very strong desire for an approval of givinostat within the entire DMD community – within both ambulant and non-ambulant groups.<br><br>This is based on three factors: |

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| | • The results of the Phase 3 EPIDYS study<br>EPIDYS demonstrated that givinostat is slowing down the progression. Results from the Italfarmaco Pivotal Phase 3 EPIDYS Study of givinostat in DMD were published in The Lancet Neurology in March 2024. The EPIDYS clinical trial met its primary endpoint: change in four-stair climb assessment from baseline to 72 weeks, which demonstrated the potential of givinostat to delay disease progression when added to corticosteroid treatment. givinostat-treated boys also showed favourable outcomes on key secondary endpoints assessed in the study.<br><br>"The trial results look promising: although this is not a cure it looks to slow down disease progression. If it can keep my son walking for longer, and enable him to climb stairs for longer, which means he can go to friends' houses or granny's for dinner, that will have a hugely beneficial effect on his life and on ours as his parent carers". -Parent of a 16-year old boy with DMD<br><br>• The personal experience of givinostat among the DMD community<br>People with DMD and parents of people with DMD share their experience of DMD and compare the progression of the disease between those who have been able to take part in a trial and those who haven't. Parents whose sons are on the trial are sharing the positive impact of being in the trial which adds to the popular perception that givinostat is, while not a cure for DMD, is slowing down its progression.<br><br>• The lack of current treatments for DMD<br>In April 2024, a survey of the DMD community undertaken by Duchenne UK, asked whether they thought there should be more treatment options for DMD, not one parent/patient respondent replied 'no'. When asked 'How do you feel about the current treatment options for DMD?', givinostat and its approval was referenced:<br><br>"I feel they are extremely limited. I really hope that givinostat gets approved in the UK very quickly." |

[5] Developing a Natural History Model for Duchenne Muscular Dystrophy, Broomfield et al, Nov 2023, https://link.springer.com/article/10.1007/s41669-023-00450-x

## Disadvantages of the technology

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| **10. What do patients or carers think are the disadvantages of the technology?** | Together with Duchenne UK, we believe that the benefit risk profile favours benefit with givinostat. Families of patients who have received givinostat suggested that there were no serious adverse events and that side effects were well tolerated. The drug, taken orally, has a horrible taste. Some had diarrhoea and one reported to us that their son was monitored for temporary decreased platelet count. As a result of still walking in their late teens, one family reported lower back pain from pressure applied to the spine from poor posture – though they also noted lower back pain was vastly more preferable than the alternative of losing ambulation. |

## Patient population

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| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | From our understanding, givinostat will benefit any patient, and is not specific to a certain mutation. |

## Equality

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| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | Many DMD patients have significant mobility issues. This should be taken into account, so no patients are denied access to a treatment because of travel requirements.<br>We are not aware of any other potential equality issues that should be taken into account, beyond those which should be considered for rare diseases in general. |

## Other issues

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| **13. Are there any other issues that you would like the committee to consider?** | No. |

## Key messages

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| **14. In up to 5 bullet points, please summarise the key messages of your submission.** | • DMD is a devastating condition, with no cure. There is a strong unmet need for effective treatments for DMD<br>• The standard medical management of DMD, corticosteroids, is accompanied with severe negative side effects<br>• Slowing the progression of the disease, producing incremental improvements, and retaining ambulation and upper limb function, would deliver large quality of life benefits to patients and their caregivers, and is highly desirable to patients and their carers<br>• There is a strong desire to access givinostat throughout the DMD community |

Thank you for your time.

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# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this submission**

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

## About you

NICE National Institute for Health and Care Excellence

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| **1. Your name** | [redacted] |
| **2. Name of organisation** | Association of British Neurologists |
| **3. Job title or position** | [redacted] |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes<br>A specialist in the treatment of people with this condition? Yes (although limited to adults)<br>A specialist in the clinical evidence base for this condition or technology? No<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | The Association of British Neurologists' is a professional membership organisation and its mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The ABN receives funding mainly from its member subscriptions and annual conference income. Additional funding from external charity organisations is received to solely fund fellowships. Additionally, the ABN receives sponsorship from pharmaceutical companies. Sponsoring companies have no input, control nor opportunity to influence the ABN. |

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| **5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company.<br>• Abbvie<br>• Alnylam<br>• Angelini<br>• argenx<br>• Biogen<br>• Eisai<br>• Eli Lilly<br>• Janssen<br>• Pfizer<br>• Roche<br>• Sanofi<br>• Teva<br>• UCB |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |

## The aim of treatment for this condition

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| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | Givinostat an oral histone deacetylase inhibitor. The drug is thought to counteract the pathogenic events downstream of dystrophin deficiency in Duchenne muscular dystrophy (DMD) (e.g. muscle inflammation and subsequent fibrosis).<br>In a recent clinical trial givinostat recipients showed less decline than placebo recipients in the time taken to perform a functional task (four-stair climb). This may well translate in to slowed rate of decline in other measures and overall function.<br>Importantly, the mechanisms of action of givinostat does not rely on the presence of a specific underlying genetic variant. |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | Whilst an application is being made to use givinostat in all people with DMD over 6 years old, I am not aware of any significant body of evidence relating to its use in adults, which is where my knowledge is. As current standard of care involves the use of steroids, similar outcome measures and treatment response criteria to those used currently should be considered. |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | There is a huge unmet need for people with DMD. Steroid treatment is the standard of care but carries a significant burden of adverse effects and is limited in effectiveness. Some gene-targeted treatments are available (in the UK, my understanding is that Ataluren is the only one with approval for use), but these can only be used in small subgroups of people with DMD according to the specific underlying genetic defect they have. |

## What is the expected place of the technology in current practice?

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| **9. How is the condition currently treated in the NHS?** | Duchenne muscular dystrophy (DMD) is a complex and progressive neuromuscular condition which requires multidisciplinary care in a specialist centre.<br><br>Multi-dimensional care is required, including consideration of: |

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| | • Neuromuscular weakness, maintaining strength and function etc, including access to appropriate physical and occupational therapy<br>• Access to medical treatments including steroids (glucocorticoids, corticosteroids), and in some instances small molecule gene-targeting medications which seek to restore the synthesis of dystrophin by allowing ribosomes to read through premature stop codons in the dystrophin gene (Ataluren).<br>• Management of endocrine issues including bone health and puberty<br>• Pulmonary management and the use of non-invasive ventilation and other support devices such as cough assist machines<br>• Cardiac management and issues relating to heart failure<br>• Gastrointestinal issues including nutritional issues and swallowing problems<br>• Access to appropriate wheelchairs and other assistance devices |
| **9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?** | Yes:<br><br>https://www.mda.org/sites/default/files/publications/DMDCareGuidelines_diagnosis-mgmt.pdf<br><br>and<br><br>https://www.mda.org/sites/default/files/publications/DMDCareGuidelines_multicare2010.pdf |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | I am not aware of any significant differences in opinion in the UK regarding the pathway of care for people with DMD. |
| **9c. What impact would the technology have on the current pathway of care?** | As a neurologist that treats only adults, I can only really make limited comments as this new treatment will most likely be mainly used in children. The median life expectancy for a person with DMD remains very low at around 28 years and many patients will remain under a paediatric specialist clinic for their whole life. |

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| | As I understand it, givinostat could be used in addition to steroids in a wide group of people with DMD, unlike the gene-targeted treatments, for example. If the effect seen in clinical trials is mirrored in clinical practice, then a slower rate of decline could theoretically be expected, potentially permitting a reduced overall steroid exposure and reduced progression to overt respiratory and/or cardiac failure.<br><br>One issue to consider is “stopping rules”. There is currently a lack of consensus on how long to continue steroid treatment for as children with DMD transition in to adulthood. Consideration may need to be given to any stopping rules relating to this new medication if it is approved. |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | My understanding is that it would be used in addition to current standard of care, with commencement during childhood. However, my experience in the treatment of children is limited and therefore I cannot comment further. |
| **10a. How does healthcare resource use differ between the technology and current care?** | The key difference to several other novel therapies in development is that givinostat could be used regardless of the exact underlying genetic defect, broadening access to a potentially effective treatment for the condition. |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | Specialist neuromuscular clinics only. |
| **10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)** | The effectiveness of therapeutic intervention in muscle wasting conditions like DMD depends on simultaneous access to high quality multidimensional care and an expert experienced care team which includes physicians, physiotherapists and occupational therapists.<br><br>Assessing the response to novel therapies in DMD and other muscle wasting conditions is complex and usually requires assessment using specialist tools which need to be completed by an expert physiotherapist with experience in the disease area. |

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| | It should be remembered that if givinostat is approved on a conditional basis where specialist outcome measures have to be performed at certain intervals, consideration should be given to the funding and provision of physiotherapists and other professionals to perform these assessments.<br><br>One additional consideration is that giviostat is an oral medication and therefore additional resources relating to hospital administration of the drug are not required. |
| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | I have limited experience in this area. The recent RCT (https://pubmed.ncbi.nlm.nih.gov/38508835/ ) would suggest benefit over placebo, but the recipients of the drug were all children and therefore I am unable to comment further as I only treat adults with DMD and other muscle wasting conditions. |
| **11a. Do you expect the technology to increase length of life more than current care?** | I don't think we have enough evidence to comment on this. |
| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | The clinical trial would suggest that the drug slows the rate of decline in certain functional measures. One might assume a knock on positive effect on HR-QOL, but as far as I am aware this has not been specifically or thoroughly assessed. |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | The treatment is only for people with DMD aged >6 years. I do not have an understanding as to why this age cut off has been selected and whether or not the treatment would be effective in younger people too. Similarly, the evidence I am aware related to commencement of treatment in childhood, so whether or not there would be a useful effect if started later in life (e.g. > age 16) is impossible to comment on. |

## The use of the technology

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| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals** | I have no comments on this. |

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| **than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | |
| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | I am not aware of specific rules, beyond the minimum age cut off (see comments above). |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | I have no comments on this. |
| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the** | As noted above, given the focus on paediatric cases in relation to use of this drug, it is difficult for me to comment. It is important to note that the drug did not *improve* performance in functional outcome measures in the clinical trial, but rather slowed the rate of decline. This should be taken in to account when assessing the impact of QOL. |

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| **way that current need is met?** | |
| **16a. Is the technology a 'step-change' in the management of the condition?** | I think it could be – the mechanism is unique as compared to steroid (and steroid-like treatments such as vamolorone) for this indication and it can be used across a wide range of patients with the disease, not dependent on the presence of a certain genetic change (which massively limits the use of other novel therapies), |
| **16b. Does the use of the technology address any particular unmet need of the patient population?** | Potentially. Steroids carry a massive burden of adverse effects and I wonder if steroid exposure could be reduced if givinostat were available. In addition, treatments beyond steroids are not available for the majority of people with DMD as they depend on the presence of a certain genetic change. Givinostat can be used across a much wider range of patients with DMD. |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | I have no comments on this. |

## Sources of evidence

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| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | I feel unable to comment on this as my experience is primarily with adults. |
| **18a. If not, how could the results be extrapolated to the UK setting?** | - |

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| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | I feel unable to comment on this as my experience is primarily with adults. |
| **18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?** | I have no comments on this. |
| **18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?** | I have no comments on this. |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No. |
| **20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE highly specialised technologies guidance [HST22]?** | No. |
| **21. How do data on real-world experience compare with the trial data?** | I don't know. |

## Equality

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| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | Convenient access to a specialist assessment and treatment centre is a major issue for people living with rare neuromuscular conditions, including DMD. There are intersectional equality issues relating to this which may explain some of the variation in care and outcomes across the UK. |
| **22b. Consider whether these issues are different from issues with current care and why.** | This is not a new issue. |

## Key messages

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| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | • Experience with the drug, and evidence from trials, is primarily with children. As such, my comments are limited given my status as a neurologist only treating adults.<br>• Givinostat appears to slow the rate of decline in some people with DMD.<br>• This may have knock on effects on other aspects of disease, potentially including overall function and QOL.<br>• Care for DMD is complex and medical therapies is only one (small) part of a large puzzle which includes issues relating to access to wheelchair services, therapy services (physiotherapy, occupational therapy, exercise etc.), respiratory and cardiac care, and bone health, as well as others.<br>• Understanding the effectiveness of treatments for neuromuscular conditions often requires the use of complex assessment tools completed by a specialist physiotherapist. Consideration should be given to the access and provision of such professionals, as well as the availability of specialist centres. |

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# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Professional organisation submission

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- Your response should not be longer than 13 pages.

## About you

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | British Paediatric Association (Muscle interest group) BPNA |
| **3. Job title or position** | [redacted] |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No<br>A specialist in the treatment of people with this condition? Yes or No<br>A specialist in the clinical evidence base for this condition or technology? Yes or No<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | The Muscle interest group is one of the 'special interest groups (SIGs)' within the BPNA. I have been chair of this group for approximately 7 years, and as a group we are mainly consultant paediatric neurologists who generally specialise in neuromuscular conditions and are part of the Northstar group and many also take part in the Duchenne muscular dystrophy (DMD) trials as well as being DMDHub sites. We also have paediatric neurology trainees who have an interest in Neuromuscular disorders and allied health professionals, such as clinical nurse specialists, neuromuscular physiotherapists and neuromuscular care advisors. |
| **5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | Not for the Muscle interest group meetings. |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |

## The aim of treatment for this condition

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| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | The main of this treatment is to slow progression of a severe progressive muscular dystrophy, and effectively shifting the timelines further to enable better quality of life and further preservation of function, such as stair climb, rise from the floor and ambulation.<br>Whilst there is no cure for this condition, at best preservation of function, and prolonging stages at certain function such as ambulatory is important both for physical health as well as mental and psychological health and also carer/parent wellbeing. |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | In DMD a preservation of ambulation and timed rise from the floor as demonstrated in this trial is clinically significant. In a severely progressive muscle wasting condition, where every year sees a loss in function, the preservation and demonstration of TRFF and 4SC being achieved 2 and 3 years post the natural history is significant and whilst all boys with DMD are different, if we can continue to delay these milestones, then this leads to boys transitioning into adulthood with improved function and ability to achieve more. |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | There is definitely an unmet need, as current treatment and management is standards of care (SoC) as per 2018 guideline (Birnkrant DJ, Bushby K, Bann et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018 Mar;17(3):251-267) monitoring and treatment with corticosteroids. |

## What is the expected place of the technology in current practice?

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| **9. How is the condition currently treated in the NHS?** | Currently in UK and NHS, these young people are treated as per the Standards of care (SoC) and we follow the NorthStar's guidance. This essentially comprises of treatment with corticosteroids, mainly daily prednisolone, as shown most efficacious in the FORDMD trial (Guglieri M et al.Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. JAMA. 2022 Apr 19;327(15):1456-1468), or intermittent dosing (or deflazacort). These doses are 0.75mg/kg Prednisolone or |

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| | 0.9mg/kg deflazacort daily. This, to date, has been the only treatment that has significantly benefitted children with DMD however there is considerable side effects that need to managed and hence in the standards of care; Bone health, growth, cataracts, gastrointestinal and endocrine side effects are proactively evaluated and treated. As part of the standards of care, cardiac and respiratory monitoring and proactive commencement of cardiac drugs and non-invasive ventilation and respiratory preventative medications are commenced early, as this has been shown to be more effective than waiting until later when cardiac/respiratory failure are established.<br>This has led to a increase in survival and shifted the timeline of loss of ambulation, time to ventilation etc. |
| **9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?** | As above – the international guidelines (updated in 2018 from the 2010 guidelines) – tri-part publication in the Lancet, endorsed by both the Northstar clinical network (clinicians) and Duchenne care UK (charity supported by clinicians in developing more detailed clinical guidelines based on the international one) |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | Yes, this is well defined pathway and followed by all neuromuscular sites in the UK and adhered to. All DMD patients should be seen in a Northstar neuromuscular centre and all consented to be a part of the Northstar database in order for us to monitor and track treatment and natural history. |
| **9c. What impact would the technology have on the current pathway of care?** | This technology would be an 'add on' to the standards of care and be in additional to the steroid treatment. This would mean that these boys would have potentially an improved outcome, both from a motor perspective, but if the timeline is shifted then this generally has an effect on spinal health and respiratory function, as well as general well being and mental health and therefore this would lead to decreased carer burden (which is often parents in these families). |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | The technology would be used as in previous question as an add on and standards of care would be continued along with steroid management. It would initially require additional appointments for blood monitoring and ECG pre-commencement of treatment. These bloods could potentially be done in the local paediatric unit if the neuromuscular centre is a long distance from the families' homes. |
| **10a. How does healthcare resource use differ** | The same resources would still be required and initially extra resources to cover blood monitoring in these patients within the first 3 months to check for platelets and lipid levels, however these children are seen in clinic |

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| **between the technology and current care?** | generally every 6 months and have many of the assessments as per the trial generally completed in clinic at each visit as well as bloods to monitor renal and bone health. |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | This should be specialist neuromuscular centre with possible outsourcing some of the blood monitoring to the local teams, this will be the secondary paediatric care as GPs do not generally arrange paediatric blood tests. |
| **10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)** | There would need to be some funding for the increased blood tests and initial increased visits, especially if drug doses need to be altered as per protocol and then rechecked. Once on a stable dose, the bloods required would then fit into the standards of care and 6 monthly hospital visits.<br>This would therefore need increased doctor or specialist nurses resources as well as out-patient availability and phlebotomy.<br>As the drug is an oral dose this would be administered at home and dispensed as per usual via pharmacy, but would in theory be via the hospital pharmacy. |
| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | As per the analysis data, we would expect in responders to see a meaningful improvement in progression of the disease and a slowing of progression to the next milestone as the data suggests an improvement in timed rise from the floor, timed 4 stair climb and loss of ambulation. |
| **11a. Do you expect the technology to increase length of life more than current care?** | Yes, this has got the potential to increase length of life and increased length of life with better function.<br>As we have seen over the last 15 years with improvements in the standards of care and the commencement of treatments earlier, this has led to improved survival and most boys, commencing on ventilation as adults and loss of ambulation later. There has been a significant reduction in scoliosis surgery (Biggar et al. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. NMD<br>Volume 16, Issue 4, 249 – 255) and this is probably attributed to steroid use and due to this staying ambulant for longer which has improved posture and scoliosis. Cochrane review in 2008 (Manzur AY et al. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003725. Update in: Cochrane Database Syst Rev. 2016 May 05;(5):CD003725).<br><br>As we continue to improve standards of care, addition of another drug that can further shift this timeline would potentially lead to adults that are surviving longer and in better condition. |

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| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | Yes, as we see a better improvement in QoL in both patients and their carers when health and function are improved. There is dramatic improvements in care giver QoL, when a young person is ambulant, or has better function and can transfer and do functionally more compared to a young person who is totally dependent and requires full support, and usually from family, which often means a parent or both giving up paid work to be a carer. |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | At present the study was designed for ambulant younger boys over the age of 6 years, however given its mode of action, it could be hypothesized that it would be beneficial to younger boys and also older non-ambulant patients, and that measurement of non-ambulatory scores, such as the PUL2. (performance of upper limb) would be helpful in monitoring the effect and stability of the young person. (Current studies are ongoing in both the younger population and non-ambulant group) |

## The use of the technology

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| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | As highlighted above, whilst this is an oral medication and dosing will be done at home via caregivers, there are additional clinical requirements that will need to be addressed and coordination of these, whether local or at the neuromuscular centre. As part of the therapy, blood tests will need to be monitored, which will need to be coordinated.<br><br>The baseline bloods and ECG including fasting triglycerides can performed at the usual neuromuscular clinic and part of usual SoC, and then the prescription made following review of the investigations.<br><br>Further bloods at FBC 2 weeks, 4, 6, 8 weeks and 3 months and 6 months (these can be done again in the usual neuromuscular clinic) would need to be arranged as well as triglycerides at 3 months and 6 months and 6 months thereafter, which is not a normal test in the SoC and would need to funded. If any of these results are abnormal, and/or require treatment doses to be altered, this would require additional testing.<br><br>These other bloods could be done locally with agreement with the local paediatric team but may need to be done via the neuromuscular centre, which for some families may be a distance. I do believe that given the interventions and tests that are needed, this would not pose an issue for families necessarily, as they would be prepared for this given the potential for delaying progression. Healthcare teams would need additional support when organising and coordinating the blood testing and monitoring. |

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| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | At present, the indication is for children with Duchenne muscular dystrophy over the age of 6 years and ambulant to start the medication.<br><br>There would be no additional testing required apart from the blood tests outlined above, as the physical assessments and NSAA are completed every 6 months as per SoC and monitoring and data entry on the Northstar database. |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | The effect of the medication, if the young person is responsive, will potentially lead to a shift in the timelines and hence ambulant for longer and hence an improvement in caregivers QoL as a young person that is ambulant and/or can transfer only needs one carer compared to non-ambulant when two carers are required. This means that as parents, often they become the carers, and if only one has to be a carer, the other has the ability to go out to work or they share the care and both have jobs. This leads to greater satisfaction and independence and has a positive impact on their mental health. Caring for your own child/young person who is continuing to deteriorate has a huge impact on personal health and wellbeing. Most carers are informal carers (often extended family), not professional and this has a huge impact.<br><br>For the young person who is ambulant or more able, but using a wheelchair for longer distances etc, they have more access, are less fatigued and can continue school, college or work, have more independence and more able to access social events if they want to and hence the potential for improved QoL. |
| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | As above, the improvement seen in the trial data on timed rise from the floor, ambulation and timed 4SC, delays progression and need for carers and 24 hour care with 2 carers once ability to transfer and the start of ventilation is seen. This medication means that in addition to the SoC that further improvements can be seen and delay of this progression improves the outcome and start time of, for example, non-invasive ventilation. Whilst there is still an unmet need of a ‘cure’, a medication that improves and prolongs quality of life with improved functional abilities and delaying the progression to 24 hour full care packages and ventilation is beneficial.<br><br>The innovation in that this a medication that can be used in all DMD populations and is not mutation specific is extremely beneficial to this population. |
| **16a. Is the technology a ‘step-change’ in the management of the condition?** | This does represent a ‘step change’. If we can prolong time in the different stages particularly the early and late ambulatory phases as well as transfer phase this means that other treatments that also may be in clinical trial would have a greater effect, as the earlier drug therapies are introduced and at a stage when the muscle has less destruction evident the more effective the therapy may be. Drug therapies, if there is no healthy muscle left, will |

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| | not have an effect and therefore preserving the muscle structure is essential for further treatment options to work to their potential. |
| **16b. Does the use of the technology address any particular unmet need of the patient population?** | As detailed above, at present the unmet need is a medication in addition to corticosteroids that delay the progression of the disease in this population. |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | The side effects are minimal, and mainly include issues regarding diarrhoea, low platelets and high triglyceride levels that may require reducing the drug dose with re-checking after reduction. This usually occurs within the initial 3-6 months of dosing. These dose changes require further blood tests, but often these children and young people are used to this intervention. |

## Sources of evidence

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| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | As with all clinical trials, in their nature will be more intense and have more datapoints, however all DMD clinical trials do refer to the standardised assessments that are done routinely in clinical practice and recorded by all Northstar centres every time a young person is seen in clinic and these routinely include the Northstar ambulatory assessment (NSAA), which includes the timed rise from the floor, ambulation and 10m walk and run. 4 stair climb (4SC) is not always routinely assessed but steps are and how they get up and down from them. This therefore means that direct comparison with Northstar data can be reviewed as this has long term natural history data on children and young people with DMD who are on steroids and their NSAA score and timed tests. |
| **18a. If not, how could the results be extrapolated to the UK setting?** | N/A |
| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | I do think that the most important outcomes were that of the 4 SC which was significantly different in the EPIDYS trial both from baseline to week 72 compared with controls and from week 48 to week 72 compared to controls.<br><br>The comparison between study 51 (open -label LTE) and the natural history control groups have demonstrate that preservation of ability to rise from the floor, climb 4 stairs and walk was extended by 2.0, 3.3 and 2.9 years |

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| | respectively in patients taking givinostat compared to control group. This has a major impact on function and activities or daily living. |
| **18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?** | N/A |
| **18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?** | As far as I am aware, the trial has been tolerated well and the side effects detected were mainly as listed above and most of these were within the first 3 months (diarrhoea, low platelet counts and high triglyceride levels). |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| **20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE highly specialised technologies guidance [HST22]?** | No |
| **21. How do data on real-world experience compare with the trial data?** | As |

## Equality

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| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | Ability to comply with doing the NSAA and other assessments as well as increased blood tests may be an issue for some children with autism and learning difficulties that can be part of Duchenne muscular dystrophy in approximately 30%, and this therefore may have an impact on these children. However in clinical care we already deal with this and these children are reviewed regularly and assessments attempted and with time and maturity they often manage these. This should not affect access to the drug. |
| **22b. Consider whether these issues are different from issues with current care and why.** | These are no different from the other aspects of care in these young people and whilst this may be difficult, they often do comply with assessments over time once they have learnt what to do with continued practice, and with play therapists are able to have their blood tests. As the drug is oral administration, parents and carers are usually very adept at giving medication, as we have seen with the other oral medications they are on. |

## Key messages

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| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | • Delay progression of the natural history of the disease.<br>• Improvement in timed tests<br>• Movement of disease progression timelines.<br>• Use with steroids and standards of care.<br>• Improve patient and carer quality of life |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

## About you

NICE National Institute for Health and Care Excellence

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| **1. Your name** | [redacted] |
| **2. Name of organisation** | British Society of Physical and Rehabilitation Medicine |
| **3. Job title or position** | [redacted] |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes<br>A specialist in the treatment of people with this condition? Yes (in adults with this condition)<br>A specialist in the clinical evidence base for this condition or technology? No<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | BSPRM is dedicated to advancing the knowledge and practice of Rehabilitation Medicine in the UK, and to promoting excellence in patient care. We bring together a multidisciplinary team of healthcare professionals, including physicians, therapists and nurses, among others, who are all passionate about improving function and quality of life for patients with long-term conditions. We focus on whole-person rehabilitation rather than organ-specific conditions. BSPRM is funded by grants, membership fees and income from training courses. |
| **5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | No |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |

## The aim of treatment for this condition

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| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | The aim of Givinostat use in DMD is to reduce disease progression and disability. |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | A slower decline or stabilisation of the North Star Ambulatory Assessment (NSAA) compared with placebo. A minimally important clinical difference in the NSAA is difficult to define as it depends on the age of the patient, their score on the NSAA at the start of treatment and individual compensatory movements. I would recommend an expert statistical opinion to explore this question further. |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | Yes. |

## What is the expected place of the technology in current practice?

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| **9. How is the condition currently treated in the NHS?** | Corticosteroids are the main disease modifying treatment currently. There are other forms of disease modifying therapies for boys with specific mutations. All the answers below are predicated on this first being used in the paediatric population with DMD as current publications concern use in DMD in that population. |

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| **9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?** | DMD Standards of Care published by the DMD care working group and North Star Clinical network. These are based on international standards of care divided into three papers:in Lancet Neurology 2018 - 17: 251 – 267; 347-361;445-455. |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | The pathway of care in the NHS is well defined, but with regional differences.<br><br>Our experience in the BSPRM is indirect as current pathways for the patients eligible for this drug (children with DMD aged 6 and above) are in paediatric services. If givinostat were to be used in the adult population the pathways are not well defined. |
| **9c. What impact would the technology have on the current pathway of care?** | I would expect it to be amalgamated into the current pathways of care. In the long term it will then lead to changes in the adult care pathway and it could be started in adult life. This is where it will have an impact on the services our specialty provides, as we would expect this technology to lead to increased survival and a lesser, but still substantial, degree of disability. |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | I would expect it to be used in the same way alongside the current pathways in paediatrics that are involved with use of corticosteroids and Ataluren for DMD. |
| **10a. How does healthcare resource use differ between the technology and current care?** | I would expect there to be need for closer follow up and monitoring initially. |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | Specialist clinics in use of disease modifying drugs initially, but as familiarity with the medication improves there may be scope to expand to other secondary care clinics for people with neuromuscular conditions. |
| **10c. What investment is needed to introduce the** | Due to different side effects and monitoring needs compared with steroids, there would be training and resource implications. |

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| **technology? (For example, for facilities, equipment, or training.)** | In the long term it will lead to a greater need for resources that will assist people with DMD in adulthood, for instance regarding condition management and rehabilitation/enablement regarding work, higher education, equipment, pADL support, housing, etc. |
| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | In the long term it is hoped it will lead to reduced disability and reduced complications of DMD, or at least delay these until a later age. Long term side effects are not yet known. It will be important that the North Star Network and its associated research projects continue to be funded in order to provide the evidence base for the long term use (or not) of Givinostat. |
| **11a. Do you expect the technology to increase length of life more than current care?** | Yes, but long term evidence will be required. |
| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | Yes, but long term evidence will be required. |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | This technology is for those with Duchenne Muscular Dystrophy, but there may be a possibility that it could help those with other muscular dystrophies and myopathies, in addition to the non muscle conditions it is currently being used in (e.g. polycythemia vera). |

## The use of the technology

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| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for** | It will be easier to administer, as it is an oral medication. It will still require monitoring because of potential side effects of thrombocytopaenia and hypertriglyceridaemia. The common side effects of vomiting and diarrhoea may mean that patients require further support, including medication, or order to |

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| **example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | continue taking givinostat. The long term effects of causing hypertriglyceridaemia are yet to be established. |
| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | I would suggest there are formal stopping and starting criteria, but would not have the specialist knowledge from clinical trials of givinostat to suggest what these should be. |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | I cannot answer this without seeing what health related benefits are included in the current QALY calculation. |
| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | As it is expected to reduce the rate of disease progression it should allow those with DMD to have greater participation in education, relationships, work, etc. Importantly, it will mean that those treated will be better able to participate in key aspects of growing into adulthood, involving exams, relationships, going to university, starting work, participating in sport and leisure, etc. All these would be expected to have a positive impact on health. |
| **16a. Is the technology a 'step-change' in the** | Yes. |

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| **management of the condition?** | |
| **16b. Does the use of the technology address any particular unmet need of the patient population?** | It should address a wide range of unmet needs at a particular age, as it will delay disease progression and disability. May of the needs associated with those are not well met at the moment – e.g.the need for effective and appropriate wheelchair provision is frequently not met and this condition should delay the time for which higher specification wheelchairs are needed; another example is effective prevention of intercurrent chest infections and pneumonia, which should not be necessary until a later age with this medication. |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | The commonest side effects of vomiting and diarrhoea have the potential to affect quality of life and condition management, and it will be important for services to respond quickly when these side effects arise so as to manage them as effectively as possible. Thrombocytopaenia is less common but will need effective management when it occurs. In some cases side effects will mean the drug cannot be continued. |

## Sources of evidence

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| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | Not directly involved in these trials, so cannot comment. |
| **18a. If not, how could the results be extrapolated to the UK setting?** | |

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| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | Mostly covered. However, different outcomes would be relevant at different stages of DMD, so NICE is considering its use in those with more advanced DMD (e.g. those who are wheelchair dependent for mobility but still have reasonable use of their upper limbs), other primary and secondary outcome measures would be more relevant. The use of the NSAA is important as it covers several domains. |
| **18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?** | |
| **18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?** | Not that I know of. |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No. |
| **20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE highly specialised technologies guidance [HST22]?** | Publication of the phase III trial: Mercuri, Eugenio, et al. "Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial." *The Lancet Neurology* 23.4 (2024): 393-403. There are also two abstract reports: Andres, D. Gomez, et al. "429P Givinostat in Duchenne muscular dystrophy: natural history comparison applying propensity score matching." *Neuromuscular Disorders* 43 (2024): 104441-300 and 43 (2024): 104441-280. |

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| **21. How do data on real-world experience compare with the trial data?** | Not known. |

## Equality

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| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | Equality of access to the drug, this could be affected by postcode and parents/carers having adequate transport to allow follow up assessment and monitoring. |
| **22b. Consider whether these issues are different from issues with current care and why.** | Likely to be similar. |

## Key messages

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| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | • Likely to improve overall quality of life by delaying and reducing disability.<br>• Will have an impact on future services for adults and children with DMD, with a greater emphasis on rehabilitation and enablement, which will need targeted workforce planning and resource use.<br>• It is important to continue the current North Star programme in order to assess the long term outcomes of using this and subsequent disease modifying technologies.<br>•<br>• |

Thank you for your time.

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal
# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]
# NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

NICE National Institute for Health and Care Excellence

## About you

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| **Your name** | [redacted] |
| **Name of your organisation** | John Walton Muscular Dystrophy Research Centre |
| **Please indicate your position in the organisation** | Department of Health and Social Care or Welsh Government in general?<br>• Commissioning services for the Department of Health and Social Care or Welsh Government specific to the condition for which NICE is considering this technology? NO<br>• Responsible for quality of service delivery in the ICB (e.g. medical director, public health director, director of nursing)? NO<br>• A specialist in the treatment of people with the condition for which NICE is considering this technology? YES<br>• A specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)? YES<br>• Other (please specify): |
| **Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry** | No |

## What is the expected place of the technology in current practice?

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| **How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion** | In the UK, there is a well established paediatric network of neuromuscular clinics (the North Star Network) that follow up patients with DMD. Within the network, patients with DMD are treated according to the published International Care recommendations for Duchenne muscular dystrophy. Moreover, a national initiative (DMD Care UK, https://dmdcareuk.org/) is a collaboration between multi-disciplinary clinical experts and patient organisations to define practice care guidelines for DMD across the UK. |

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| **between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?** | Current care recommendations include a multi-disciplinary approach to DMD, with involvement from different specialists (neuromuscular specialist, physiotherapy, cardiology, respiratory clinicians, endocrinologist, orthopaedic surgeons, psychologist, social care advisor, dietician/nutritionist).<br><br>Neuromuscular management (the target of the assessed technology) currently include physiotherapy input and the use of corticosteroids (prednisone or deflazacort). The mechanism of action of corticosteroids in DMD is not fully understood but they reduce inflammation through a specific pathway (NFKbeta inhibition). Corticosteroids have been shown to improve muscle strength and function over a certain period of time; they delay respiratory and cardiac involvement and reduced the likelihood to required orthopaedic interventions (spinal surgery). Corticosteroids however are associated with several side effects (e.g. weight gain, stunting of growth, bone fragility and increased risk of fractures etc) which require monitoring and interventions.<br><br>Corticosteroids are routinely prescribed to children with DMD across the UK, according to the international care guidelines. There is a national agreement on time of treatment initiation (between the age of 4-6 years); there is an ongoing effort in harmonising prescription across the UK, however currently there is still some discrepancy on doses and regimens used across different centres (daily versus intermittent regimen).<br>There are increased evidences to support the continuation of corticosteroids after loss of ambulation and in adults with DMD however treatment in the older patients is less harmonised with same centres discontinuing corticosteroids at the time or after transition into adult services. This is partially due to management of side effects.<br><br>A new, dissociative corticosteroid, vamorolone, is currently under evaluation by NICE. Vamorolone is suggested as alternative to traditional corticosteroids.<br><br>Ataluren is currently available in the UK as treatment for DMD. Due to the mechanism of action (reading through stop codon mutations), ataluren is a treatment option only for a subgroup of patients with DMD, carrying a stop codon mutation in the DMD gene (and representing approximately 8-10% of the DMD population)<br><br>The assessed technology, givinostat, is not suggested as alternative to corticosteroids (or vamorolone) but as additional treatment. It has been tested in clinical trials in association with stable corticosteroid treatment, without safety concerns. |

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| | Although to my knowledge the co-administration of givinostat and ataluren has not been tested, based on the mechanism of action, the two drugs act on different pathways and could be given in association.<br><br>There are no other treatments currently available for patients with DMD targeting the skeletal muscles. Exon skipping approaches using antisense oligonucleotides are not approved although there are patients currently receiving some of these therapies through compassionate use programs. Similarly to ataluren, in principle these drugs could be administered in association with Givinostat due to their different mechanism of action. The same would apply to gene therapy approaches which are currently in clinical trials. |

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| **To what extent and in which population(s) is the technology being used in your local health economy?**<br>**Is there variation in how it is being used in your local health economy?**<br>**Is it always used within its licensed indications? If not, under what circumstances does this occur?**<br>**What is the impact of the current use of the technology on resources?**<br>**What is the outcome of any evaluations or audits of the use of the technology?**<br>**What is your opinion on the appropriate use of the technology?** | The technology has been so far only used in clinical trial setting. The placebo-controlled pivotal study enrolled patients age 6 and older and still ambulant. The study was followed by an open label extension study, only open to patients previously enrolled in the pivotal study.<br>Within the ongoing extension study, we have been treating older, non-ambulant patients with no specific concerns.<br>There are other two ongoing clinical trials with Givinostat in DMD one for children age 2-6 and one for non ambulatory patients age 9-18 years. We have not started enrolment in these two studies and therefore do not have direct experience within this population.<br><br>Based on the limited personal clinical trial experience, givinostat is well tolerated; patients has reported good compliance and agreed to continue receiving the technology within the extension study. The extension study has been contributing to the generation of safety data in a wider population compared to the one included in the pivotal study. I do not have major concerns regarding the safety profile of givinostat while recognising that closer safety monitoring is required and dose adjustment might be needed in some cases.<br><br>The mechanism of action is not mutation-specific as givinostat actsm on the downstream effect of the lack of dystrophin in skeletal muscles. This means that potentially all patients with DMD could receive and benefit from givinostat. The mechanism of action and the published results of the clinical trial demonstrated a benefit of givinostat in DMD but the magnitude of the effect is limited to slowing down the natural progression of the condition more than stopping or improving the clinical course. It is expected the drug to be more beneficial in younger patients with preserved muscles (less severe pathology) however the clinical trial has reached its primary endpoints without specific stratifications on age or residual muscle function. While data on older patients are collected, I would not expect a major effect of the drug in advanced cases when muscles are largely replaced by fatty-fibrotic tissue.<br>Givinostat could be an interesting approach to combine with other, more disease specific, therapies (e.g. gene therapy, exon skipping) to |

**Potential impact on the NHS if NICE recommends the technology**

| | |
|---|---|
| **What impact would the guidance have on the delivery of care for patients with this condition?** | Givinostat is an oral medication which can be taken by patients in their home setting. Patients with DMD (paediatric and adults) are routinely follow up at a neuromuscular centre every 6 months, according to the Standards of care. This frequency of evaluation would be adequate to monitor efficacy of new technologies. However, safety monitoring will require more frequent assessments, especially at the time of treatment initiation and for the first 3-6 months, which are not currently part of the routine care and will therefore have an impact on clinical services (medical and nurse time).<br><br>Moreover, based on the guidance, a relatively large number of patients with DMD could be eligible to receive the technology. Due to the lack of treatment options, there is an interest from the patient and clinician community to offer the best treatment available in a time manner. This means that at the time of approval, clinical services will need to arrange for increased number of appointments to offer the treatment and to allow safety monitoring. Prioritisation guidelines will need to be developed and coordination of these appointments planned and supported. |
| **In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?** | DMD is a rare disease and all paediatric patients are followed up at a specialist neuromuscular centre (North Star Centres). The technology should be used in specialised setting, with knowledge and expertise in management of patients with DMD and their complications. In view of the prevalence of DMD it is unrealistic that primary and secondary care will become familiar with the technology. Primary and secondary care could support with the safety monitoring (e.g. support the collection of regular blood tests) however results should be interpreted by the specialist. Please note venepuncture in children with DMD can be difficult and several primary care settings are unable to provide this service. Venepuncture in adolescents and adults with DMD can be even more difficult.<br><br>In addition to pharmacy for drug preparation, as mentioned above, closer monitoring of patient for safety will require additional appointments, likely in hospital setting (e.g. facilities and nurse time), medical time to oversight and lab support (only vitamin D is checked annually in patients with DMD as per SoC); admin time to support the coordination of the appointment. Depending on the indication, it is possible that several patients will become eligible to receive the technology at the same time. Service support for this will be required. |

| | |
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| | |
| **Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).** | Listed above<br>- Pharmacy cost including possible requirement to deliver study drug to home/closer pharmacy after receiving results from clinical assessment to confirm safety profile<br>- Facility cost (clinic)<br>- Nurse time for safety monitoring<br>- Clinician time for establishment of treatment and safety monitoring<br>- Lab cost<br>-<br><br>Other safety and efficacy assessment will follow under routine clinical care. |
| **Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?** | Unlikely |
| **Would there be any need for education and training of NHS staff?** | The technology is an oral preparation that the subject can take in the home setting.<br><br>The technology however has so far only been used within clinical trials and therefore a limited number of clinicians in specialised centres only are familiar with the safety profile of the technology. Some training on the safety profile of the technology will be required but I would not anticipate major training needs. |

## Equality

| | |
|---|---|
| **Please let us know if you think that this appraisal:**<br>**Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced**<br>**Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**<br>**Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.** | No concerns |
| **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** | |

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

## Other issues

| | |
|---|---|
| **Please include here any other issues you would like the appraisal committee to consider when appraising this technology** | |

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# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]: A Single Technology Appraisal

Produced by: Bristol Technology Assessment Group, University of Bristol

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**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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**Contributions of authors**

CLM, ET, DC, CC and HP summarised and critiqued the clinical effectiveness data reported within the company's submission. HP and HT critiqued the statistical aspects of the submission. AS and HT critiqued the health economic analysis submitted by the company. CC critiqued the company's search strategy and SLRs. All authors were involved in drafting and commenting on the final report.

[redacted]

[redacted]

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# Abbreviations

| Abbreviation | Definition |
|---|---|
| 1L | One litre |
| 4SC | Four Stair Climb |
| 6MWT | Six-Minute Walking Test |
| AE | Adverse Event |
| AFT | Acceleration Factor |
| AIC | Akaike Information Criterion |
| BMI | Body Mass Index |
| BNF | British National Formulary |
| BSA | Body Surface Area |
| BOI | Burden of Illness |
| CI | Confidence Interval |
| CINRG | Cooperative International Neuromuscular Research Group |
| CRD | Centre for Reviews and Dissemination |
| CRO | Contract Research Organisation |
| CS | Company Submission |
| DCO | Data Cut-Off |
| DMD | Duchenne Muscular Dystrophy |
| DNHS | Duchenne Natural History Study (DNHS) |
| EAG | Evidence Assessment Group |
| ECG | Electrocardiogram |
| ECM | Established Clinical Management |
| ECRF | Electronic Case Report Form |
| EK | Egen Klassifikation |
| EMA | European Medicines Agency |
| EQ-5D-5L | EuroQol 5 dimensions (standardised instrument for use as a measure of health outcome |
| ESS | Effective Sample Size |
| FEV | Forced Expiratory Volume |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| HHM | Hand Held Myometry |
| HR | Hazard Ratio |
| HRQoL | Health-Related Quality of Life |
| HST | Highly Specialised Technology |
| HTMF | Hand-to-mouth Function |
| HTA | Health Technology Assessment |
| HUI | Health Utilities Index |
| ICER | Incremental Cost Effectiveness Ratio |
| ICMJE | International Committee of Medical Journal Editors |

| | |
|---|---|
| IPD | Individual Participant Data |
| IQR | Inter Quartile Range |
| ITC | Indirect Treatment Comparison |
| ITT | Intention To Treat |
| KM | Kaplan-Meier |
| LOA | Loss of Ambulation |
| LYG | Life Year Gained |
| MAIC | Matched-Adjusted Indirect Comparison |
| MFMS | Motor Function Measure Scale |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MMF | Mycophenolate Mofetil |
| MRS | Magnetic resonance spectroscopy |
| NE | Not evaluable |
| NHM | Natural History Model |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NI | No Information |
| NIV | Non-invasive Ventilation |
| NR | Not Reported |
| NSAA | North Star Ambulatory Assessment |
| OLE | Open-Label Extension |
| PedsQL | Pediatric Quality of Life Inventory |
| PEF | Peak Expiratory Flow |
| PODCI | Paediatric Outcomes Data Collection Instrument |
| PSM | Propensity Score Matching |
| PUL | Performance of Upper Limb |
| PSS | Personal Social Services |
| PY | Probably Yes |
| PN | Probably No |
| QA | Quality Assurance |
| QALY | Quality-Adjusted Life Year |
| RCT | Randomised Controlled Trial |
| REF | Research Excellence Framework |
| RoB2 | Risk of Bias 2 tool |
| ROBINS-I | Risk of bias in non-randomized studies of interventions |
| ROBIS | Risk Of Bias In Systematic reviews |
| RWE | Real-World Evidence |
| SAE | Serious Adverse Event |
| SAS | Safety Analysis Set |
| SD | Standard Deviation |
| SE | Standard Error |

| | |
|---|---|
| SF | Short Form Health Survey |
| SLR | Systematic Literature Review |
| SOP | Standard Operating Procedure |
| SPC | Summary of Product Characteristics |
| STA | Single Technology Appraisal |
| TAG | Technology Assessment Group |
| TEAE | Treatment Emergent Adverse Event |
| TSD | Technical Support Document |
| TTO | Time Trade-Off |
| UITC | Unanchored Indirect Treatment Comparison |
| UK | United Kingdom |
| US | United States |
| VLFF | Vastus Lateralis Fat Fraction |

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# 1 EXECUTIVE SUMMARY

This summary provides An overview of key issues identified by the evidence assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

- Section 1.1 provides an overview of the key issues.
- Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER.
- Sections 1.3 to 1.6 explain the key issues in more detail.

Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report. (See Section 2)

## 1.1 Overview of the EAG's key issues

All issues identified represent the EAG's view, not the opinion of the National Institute of Health and Care Excellence (NICE). Table 1 provides an overview of the EAG's key issues:

**Table 1: Summary of key issues**

| ID6323 | Summary of issue | Report sections |
|---|---|---|
| **Key Issue 1** | Have comparators been appropriately specified in the submission? | 2.1 and 2.2 |
| **Key Issue 2** | Definition of 'ambulant' status and implications for generalisability to UK clinical practice | 2.2, 3.3.1.2, 3.3.2.2, 3.4.2.1, 3.4.2.2 |
| **Key Issue 3** | Post-hoc selection of givinostat OLE patients | 3.4.2.1 |
| **Key Issue 4** | Source of data to inform comparative treatment efficacy | 3.4.2.2 |
| **Key Issue 5** | What is the impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints? | 3.4.5, 3.4.3, 9.6 |
| **Key Issue 6** | Use of 1.5% discounting | 4.2.5 |
| **Key Issue 7** | Overestimation of caregiver utility impact | 4.2.7 |
| **Key Issue 8** | Costs and quality of life assumed the same in the full ventilation states and night ventilation states | 4.2.7 and 4.2.8 |
| **Key Issue 9** | Overestimation by NHM of survival and DMD clinical progression events | 4.2.6 |
| **Key Issue 10** | Mismatch of HERCULES NHM and available RCT data on givinostat | 3.4 and 4.2.2 |
| **Key Issue 11** | Implementation of treatment effect within the economic model | 3.4, 4.2.2 and 4.2.6 |

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are to apply 3.5% discounting to costs and effects throughout the time horizon, include caregiver QALYs for the ECM arm, modify the caregiver utility impacts, align the number of caregivers with expected increases in need with disease severity, apply costs and utilities that reflect increased impact of DMD when moving from only night ventilation to full ventilation, including givinostat monitoring costs, including tertiary and medical aid costs not captured in the company submission, using CINRG DHNS rather than the UK registry study for the source of comparative treatment efficacy, and applying the indirect treatment comparison hazard ratio directly to the model in a way that avoids double counting of treatment effects.

## 1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Delaying loss of ambulation and thus progression to more severe states of DMD with only hand to mouth function, increasing use of ventilation, and death.
- Reducing the impact on caregivers

Overall, the technology is modelled to affect costs by:

- Incurring treatment costs, monitoring costs, and administration costs
- Reducing costs from use of ventilation and spinal fusion surgery

The modelling assumptions that have the greatest effect on the ICER are:

- The selection of comparator data for the unanchored indirect treatment comparison
- The method by which the treatment effect is implemented in the model
- The methods of including impact on caregiver quality of life
- The choice of long-term discount rate to effects (1.5% in company base case, 3.5% in EAG preferred assumptions)

## 1.3 The decision problem: summary of the EAG's key issues

**Key Issue 1: Have relevant comparators been specified in the submission?**

| Report section | 2.1 and 2.2 |
|---|---|
| Description of issue and why the EAG has identified it as important | The NICE scope specifies Established Clinical Management (ECM) as a comparator for the appraisal. ECM includes corticosteroids, which most patients will take (the company submission cites research stating 73% patients in UK have been prescribed a corticosteroid). On 16/01/25 NICE issued new guidance on use of a modified |

| | |
|---|---|
| | corticosteroid for DMD, vamorolone, which has a preferable side effect profile to existing corticosteroids. The implications of vamorolone displacing current corticosteroids in ECM for DMD, have not been considered in the current submission. However, the EAG also note that TA1031 expressed uncertainty regarding the clinical effectiveness of vamorolone compared to prednisone. EAG clinical advice suggested newly diagnosed DMD patients may be more likely to be offered vamorolone instead of standard corticosteroids but existing patients may prefer not to switch if established on their current regimen. EAG clinical advice also noted that, in respect to clinical practice, the comparator for the appraisal is ECM and that givinostat would be given alongside any approved corticosteroid.<br><br>The EAG are satisfied that ataluren is not an appropriate comparator, given the population considered in this appraisal. The majority of patients eligible for givinostat would not be eligible for ataluren. |
| What alternative approach has the EAG suggested? | Vamorolone was approved after the company Submission (CS) was filed (04/12/24) and after EAG clarification questions (19/12/24). However, as vamorolone has the potential to displace current corticosteroid use as part of ECM in the UK, the EAG consider that ECM resource use and utilities estimates included in the CS should be updated to reflect this in scenario analyses. Plausible scenarios include: only newly diagnosed patients receiving vamorolone, those diagnosed within 1-2 years switching to vamorolone, and all DMD patients switching to vamorolone.<br><br>The EAG also consider that it is possible that the natural history of ECM might be modified by the use of vamorolone. As the natural history model (NHM) used in the CS was based on real world data and clinical opinion, prior to vamorolone approval, the company's NHM would no longer be valid and would need to be reconsidered. |

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| What is the expected effect on the cost-effectiveness estimates? | Including vamorolone as an alternative to standard corticosteroids (prednisone or deflazacort) when delivered as part of ECM could potentially impact costs and benefits of givinostat compared to ECM. As such, ICERs reported in the CS would no longer be relevant. However, the EAG is not able to predict whether the ICER would increase or decrease. |
| What additional evidence or analyses might help to resolve this key issue? | Further analyses exploring plausible clinical scenarios relating to the use and probable market share of vamorolone in place of standard corticosteroids. |

### Key Issue 2: Definition of 'ambulant' status and implications for UK clinical practice

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| Report section | 2.2, 3.3.1.2, 3.3.2.2, 3.4.2.1, 3.4.2.2 |
| Description of issue and why the EAG has identified it as important | The NICE scope and givinostat marketing authorisation cover ambulant and non-ambulant patients. The CS focuses on ambulant patients (at initiation of givinostat). There is no agreed definition of ambulatory status in DMD. Categorisation of a patient as ambulant/ non-ambulant may depend on the assessment or measured used. The EAG heard from clinical advisors that measurement of ambulation in carefully controlled clinical studies may differ from measurement in practice settings. There may also be variability in assessment across practice settings. |
| What alternative approach has the EAG suggested? | At clarification (questions A1 and A3), the EAG acknowledged that there is uncertainty and no consensus on preferred measures of ambulatory or functional status or agreement how measures map to the ambulatory phases of DMD. However, there is a lack of transparency in the CS as to how this uncertainty may impact on transition between health states in the economic model. Particularly in the data sources informing estimates for the ECM arm in the uITC (Key Issue 3 and Key Issue 4) |
| What is the expected effect on the cost-effectiveness estimates? | Unclear. Ambulatory status is reflected in key health states in the economic model. Definitions of non-ambulant varied across the clinical study and 'real world' data sources used to estimate the givinostat vs ECM treatment effect for age at loss of ambulation (LOA) (a key clinical efficacy outcome informing the model). |

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| What additional evidence or analyses might help to resolve this key issue? | Further clarity on definition of non-ambulant in the ECM and givinostat data sets and in how late ambulant/early non-ambulant patients will be identified in practice. The impact of using different measures of ambulation or thresholds for ambulant/non-ambulant could also be considered in the company submission. |

## 1.4 The clinical effectiveness evidence: summary of the EAG's key issues

**Key Issue 3 Post-hoc selection of givinostat patients from OLE study**

| Report section | 3.4.2.1 |
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| Description of issue and why the EAG has identified it as important | Data sources informing the unanchored indirect treatment comparison (uITC) are a post hoc subset from the company's OLE study (with IPD) and aggregate data from a UK registry study (See also **Key Issue 4).**<br><br>All participants in OLE received givinostat. However, three groups are distinguished depending on previous study enrolment and givinostat use: 'givinostat', 'delayed givinostat' and 'naïve givinostat'. A post hoc subset of OLE participants are included in the uITC. The EAG note that age at LOA in the 'naïve' group is later than that in the 'delayed' group. However, the company excludes the 'delayed' group and includes the 'naïve' group in the uITC (despite both groups not having received givinostat previously and both meeting inclusion criteria for the study of origin -EPIDYS).<br><br>The 'givinostat' group is subdivided into those enrolled in EPIDYS and those from an earlier company study (Study 43). As noted in **Key Issue 5** the company's rationale for preferring the uITC over the EPIDYS RCT includes the need for data with a longer follow up time. Previous participants in Study 43 have the longest time on treatment of all company studies. |
| What alternative approach has the EAG suggested? | An alternative approach would be to include all patients that were included in the OLE in the uITC. This would avoid potential selection bias introduced by selecting subgroups of patients post-hoc. |

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| What is the expected effect on the cost-effectiveness estimates? | It is unclear what impact including all patients in the OLE would have on the ICER, but given that excluded patients typically have earlier age at LOA we expect that it would reduce the efficacy of givinostat and so increase the ICER. |
| What additional evidence or analyses might help to resolve this key issue? | A sensitivity analysis that includes all patients in the OLE in the uITC, and demonstrates the impact of this on the ICER, would help to resolve this issue. |

### Key Issue 4: What is the most appropriate source of data to inform comparative treatment efficacy?

| Report section | Section 3.4.2.2 |
|---|---|
| Description of issue and why the EAG has identified it as important | The EAG agree that re-weighting IPD through MAIC methods can theoretically reduce observed imbalances in patient characteristics across groups. However, for estimates to be valid, *all* prognostic factors and effect modifiers should be balanced between groups. A single matching variable (Age at start of corticosteroid) is used in the company's MAIC. The base-case source of data for the MAIC (the UK registry study) is likely to be imbalanced in prognostic factors:<br>• Availability of baseline characteristics for matching (only age at corticosteroid initiation was available)<br>• The type of corticosteroid used likely differs and efficacy between them may differ (prednisolone is commonly used in the UK, deflazacort is predominantly used in EPIDYS/OLE)<br>• Difference in inclusion/exclusion criteria between trial and registry studies |
| What alternative approach has the EAG suggested? | The company report a sensitivity analysis using data from the CINRG DHNS registry, which is matched on two additional factors (age at diagnosis and proportion of patients with deflazacort use >12 months). These additional factors are very important prognostic factors, and their impact on the results after weighting is to attenuate the effect of givinostat versus ECM on age at LOA (and subsequently on age at NIV and age at FVC<1L). Furthermore the EAG believe that CINRG DHNS may be more closely balanced to EPIDYS/OLE in terms of |

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| | other unobserved prognostic factors than the UK registry study. |
| What is the expected effect on the cost-effectiveness estimates? | Using CINRG DHNS as the evidence source to estimate comparative treatment efficacy in ECM reduces the efficacy of givinostat versus ECM. This increases the ICER. |
| What additional evidence or analyses might help to resolve this key issue? | A sensitivity analysis that presents the ICER using the MAIC results compared to CINRG DHNS would help resolve some uncertainty. However, the uncertainty around whether all important prognostic factors and effect modifiers have been balanced in the uITC would likely remain an issue. |

### Key Issue 5: What is the impact of bias arising from the lack of randomised comparisons for key outcomes at longer-term timepoints?

| Report section | Sections 3.4.5, 3.4.3, 9.6 |
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| Description of issue and why the EAG has identified it as important | The company's main study (EPIDYS) provides randomised evidence for effectiveness and safety outcomes at 18 months follow-up, which is insufficient to provide evidence on longer-term outcomes. A non-randomised, single arm extension study (OLE), is also reported with longer term follow-up. The OLE study provides evidence on age at LOA, but not on the other two endpoints used to inform the economic model, age at NIV or age at forced vital capacity <1L (FVC <1L).<br>In the absence of a randomised comparison, the CS uses an unanchored indirect treatment comparison (uITC). uITCs are observational comparisons as they rely on assuming that all prognostic factors and effect modifiers are balanced in both groups. The EAG do not believe that this is likely to have been achieved. The EAG use the ROBINS-I tool to assess the risk of bias in the 3 endpoints of interest and considers them to be at an overall critical risk of bias (See also Key Issue 3 and 4) |

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| What alternative approach has the EAG suggested? | An alternative approach could utilise the randomised treatment effects on functional measures (e.g. four stair climb [4SC]) and use these to predict outcomes within the target population. However, using these in the current economic model structure would require using them as surrogates to predict the longer-term outcomes, which is likely to introduce a different set of assumptions and uncertainties. But the EAG believe this to be a more robust approach that could incorporate individual patient characteristics to account for patient heterogeneity.[1] |
| What is the expected effect on the cost-effectiveness estimates? | Since uITC are observational comparisons they rely on assuming all prognostic factors and effect modifiers are balanced. The EAG do not believe this is likely to hold in the CS, and the uITC effect estimate for givinostat versus ECM is at high risk of bias and may overestimate effects. If effects from randomised comparisons were attenuated for key outcomes then ICER estimates would be larger than those reported in the CS. |
| What additional evidence or analyses might help to resolve this key issue? | An alternative approach would have been to use the randomised outcomes reported in EPIDYS as surrogates for the economic model outcomes, to ensure that the randomised treatment effect (balanced for prognostic factors) was extrapolated into the longer-term. |

## 1.5 The cost-effectiveness evidence: summary of the EAG's key issues

### Key Issue 6: Use of 1.5% discounting

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| Report section | Section 4.2.5 |
| Description of issue and why the EAG has identified it as important | The company uses a 1.5% discount rate for benefits beyond 30 years (and argues for a 1.5% discount rate for benefits for the whole time horizon). This is contrary to NICE's reference case. The company, in clarification question B23 argued that DMD is a condition that severely impacts quality of life. However, the EAG notes that, as reported in CS, Table 37, the vamorolone and ataluren NICE appraisals use a 3.5% discount rate for the whole time horizon as base case, as do the hypothetical models of Landfeldt 2017 and Broomfield 2024, so 3.5% has been accepted in DMD.[2-5] The company argues that 1.5% is more relevant for givinostat |

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| | than for vamorolone and ataluren due to the long-term benefits expected with givinostat, including after discontinuation, due to delayed LOA. The EAG notes that there is no evidence of this long-term benefit from either RCT or cohort studies. EAG clinical advice was that the long-term benefit of givinostat, including beyond its discontinuation, was unknown. |
| What alternative approach has the EAG suggested? | The EAGs preferred base case is to apply 3.5% discounting to benefits (and costs) over the full time horizon of the model. |
| What is the expected effect on the cost-effectiveness estimates? | The deterministic ICER increases from [redacted] in the company's base case to [redacted] when 3.5% discount factor is applied to costs and benefits over the long-term. |
| What additional evidence or analyses might help to resolve this key issue? | Long-term evidence on the benefit in DMD of givinostat after discontinuation of treatment. |

### Key Issue 7: Overestimation of caregiver utility impact

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| Report section | Section 4.2.7 |
| Description of issue and why the EAG has identified it as important | Clarification question B13.<br><br>The company's base case accounts for caregiver HRQoL using the "increments relative to the midway health state approach" which results in no caregiver QALYs being accrued in the ECM arm. This method results in a faster rate of carers' QALYs accruing over shorter periods of time in comparison to the disutility method. The latter method is preferred by the EAG as it anchors at the early ambulatory health state and represents progressively worsening quality of life in subsequent health states.<br><br>The disutility method has the added benefit of being directly compatible with utility values used in other appraisals of DMD. While the company rely on a vignette study to calculate utility decrements relative to the general population. The EAG prefer utility decrements relative to the early ambulatory health state from the BOI study, which were also preferred in TA1031, the appraisal for vamorolone.<br><br>The EAG prefers modelling an increasing burden on caregivers and increasing the number of caregivers |

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| | as opposed to the company's assumption of fixed burden on caregivers regardless of disease severity . |
| What alternative approach has the EAG suggested? | Disutility method to account for caregiver QALYs for ECM arm.<br>Caregiver utility decrements from BOI study (TA1031).<br>Accounting for increasing burden of care (no. of caregivers) according to disease severity. |
| What is the expected effect on the cost-effectiveness estimates? | Including carer quality of life using the disutility method leaves the deterministic ICER unchanged at [redacted].<br>Using the caregiver utility decrements accepted for decision making in TA1031 increases the deterministic ICER from [redacted] to [redacted].<br>Varying the number of caregivers according to severity of disease increases the deterministic ICER from [redacted] to [redacted]. |
| What additional evidence or analyses might help to resolve this key issue? | Studies of caregiver burdens in DMD would be beneficial to resolve these uncertainties. |

### Key Issue 8: Costs and quality of life assumed the same in the full ventilation states and night ventilation states

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| Report section | Sections 4.2.7 and 4.2.8 |
| Description of issue and why the EAG has identified it as important | The base case company submission assumes costs and utilities for states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") to be the same. The EAG considers that this does not account for cost and utility impacts of moving from only night time ventilation to needing full ventilation.<br><br>In response to a clarification question (B17) the company provided justification that this was due to limited data, and due to the HERCULES CPRD study, which provided state costs, not separating the extent of ventilation.<br><br>The company provided a scenario with multipliers to allow the costs and utilities to vary between states 7 and 8. This used cost multipliers from a HERCULES Burden Of Illness (BOI) study and utility multipliers from Landfeldt 2017.[5, 6] |

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| What alternative approach has the EAG suggested? | The EAG prefers costs and utilities to come from the BOI study in its base case. This was informed by a Delphi panel that measured quality of life for patients and caregivers in the UK using EQ-5D as part of Project HERCULES. State definitions align with those of the company model, including separate estimates for states 7 and 8. |
| What is the expected effect on the cost-effectiveness estimates? | Using the BOI costs from TA1031 and BOI utilities in CEM decreases the deterministic ICER from [redacted] to [redacted]. |
| What additional evidence or analyses might help to resolve this key issue? | Detailed costing and utility studies could be developed to inform these two states, but this is not requested of the company. |

### Key Issue 9: Overestimation by NHM of survival and DMD clinical progression events

| Report section | Section 4.2.6 |
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| Description of issue and why the EAG has identified it as important | The EAG notes that the updated NHM underestimates survival compared to clinical opinion at ages 15, 20, 25, 30, and 35, only matching at 40 and 50 years (Table 24). The EAG also notes that it consistently underestimates the age for DMD patients of starting ventilation, starting full time ventilation and death compared to UK real world data (Table 25). The EAG considers that this could overestimate the benefit of givinostat as the natural history (and thus potential for benefit) is greater. |
| What alternative approach has the EAG suggested? | The EAG identifies that this issue was due to the company's updated NHM only being calibrated, using SOLVER, to 50 year survival estimated by clinical experts (2.8%) and median age at loss of ambulation (12.1 years, as reported by UK real world data).<br><br>The EAG explored calibration to the best available survival estimates at ages 10, 20, 30, and 40, and also to UK real world data on median age starting ventilation (18.1 years) and starting full time ventilation (20.5 years). UK real-world data (in the stopped GCS group) were used at age 10 (100%), 20 (97%) and 30 (29.8%). This real-world data was limited to patients up to age 38 giving a potentially unrealistic estimate for age 40 survival (0.6%). Instead the clinical feedback estimate at age 40 (12.3%) was used. |

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| | However, the EAG noted that calibration did not result in a close match to the observed data and chose not to use this modification to the NHM in its preferred assumptions. |
| What is the expected effect on the cost-effectiveness estimates? | Calibrating the NHM on additional datapoints increase the deterministic ICER from [redacted] to [redacted]. |
| What additional evidence or analyses might help to resolve this key issue? | Further cohort studies on natural history of DMD reporting on both survival and DMD milestones (i.e., loss of ambulation, starting of ventilation, starting of full ventilation). |

### Key Issue 10: Mismatch of HERCULES NHM and available RCT data on givinostat

| Report section | Section 3.4 and Section 4.2.2 |
|---|---|
| Description of issue and why the EAG has identified it as important | The EAG notes that the HERCULES model structure transition probabilities cannot be directly informed by the primary outcome of EPIDYS (i.e., mean change in the time taken to complete a standard four-stair climb between baseline and 18 months). This leads to the model relying on non-randomised evidence to inform treatment effects, via an uITC, which the EAG has rated as being at critical risk of bias (**Key Issue 5).**<br><br>The EAG notes that there are two reasons for not building a model on the EPIDYS primary outcome. Firstly, it is not straightforward to represent the continuous outcome as a health state (e.g., categories of time to complete the four-stair climb) or event (e.g., is the event a specific increase in time to complete the climb), nor to estimate utilities for these events. Secondly, if the placebo arm of EPIDYS is not accepted as representative of baseline natural history, an external control would be needed (see Section 3.3.1.3). This would be a challenge as EAG clinical advice indicated that the primary outcome of EPIDYS (4SC) is less frequently measured in clinical practice settings due to its requiring four steps for measurement. The EAG therefore considers the use of HERCULES to be a good conceptual representation of DMD and would be expected to better link to available data from external controls. |

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| What alternative approach has the EAG suggested? | The EAG suggests an alternative model structure using continuous outcomes as a health state (e.g., categories of time to complete the 4SC) or event (e.g., is the event a specific increase in time to complete the climb). The EAG considers that this would match the EPIDYS trial primary outcome.<br><br>However, the EAG also notes disadvantages to this approach, including the difficulty in estimating costs and utilities, and in matching to an external control if the control arm of EPIDYS is not viewed to be representative of clinical practice. The HERCULES model structure has furthermore been accepted in prior appraisals. In conclusion, the EAG may accept the HERCULES structure but notes its significant limitations. |
| What is the expected effect on the cost-effectiveness estimates? | It is not feasible to change the submitted company model to focus on the EPIDYS primary outcome.<br><br>The EAG considers changing the model structure to have an unknown impact on the cost-effectiveness results. |
| What additional evidence or analyses might help to resolve this key issue? | Further clarification on the relevance of the EPIDYS control arm to clinical practice would clarify if the model should be built around this trial. |

### Key Issue 11: Implementation of treatment effect within the economic model

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| Report section | Sections 3.4, 4.2.2 and 4.2.6 |
| Description of issue and why the EAG has identified it as important | The company's model applies hazard ratios for givinostat versus ECM to multiple transition probabilities. These hazard ratios are informed by data from the uITC for age at LOA, age at NIV and age at FVC<1L.<br><br>However, for givinostat, age at NIV and age at FVC <1L are not available in the OLE, and they are therefore estimated by applying acceleration factors derived from the UK registry study to age at LOA for givinostat. The results are nested within each other (e.g. age at FVC <1L incorporates both time to LOA and time to NIV). Results estimated for each of the outcomes capture exactly the same mechanism for the treatment effect due to the way in which they are derived (from age at LOA in givinostat patients, using acceleration factors). Therefore, applying multiple hazard ratios that capture the same |

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| | mechanism, to different transition probabilities in the economic model, is likely to double count the benefits of givinostat |
| What alternative approach has the EAG suggested? | The EAG suggests applying hazard ratios for age at LOA directly to the NHM. This assumes that givinostat only has a treatment effect on LOA and that the impact on later outcomes is due only to delayed LOA. This aligns with the position stated by the company in CS Section B.3.8 and B.3.3.4, and reiterated in response to clarification questions B3 and B4, that givinostat only has an impact on LOA and that benefits on later progression are due to delayed LOA. |
| What is the expected effect on the cost-effectiveness estimates? | The EAG explored the application of MAIC hazard ratios (using UK Registry as the comparator) to only the transition from State 2 (Late ambulatory) to State 3 (Transfer) and that the impact on later health state occupancy (i.e., outcomes) is due only to delayed LOA in Scenario 10. The deterministic ICER increases from [redacted] in the company's base case to [redacted] under this assumption. |
| What additional evidence or analyses might help to resolve this key issue? | Studies estimating comparative treatment efficacy for givinostat versus ECM for age at NIV and age at FVC <1L might help to resolve this issue, though the EAG acknowledge the challenges of collecting long-term comparative evidence in this population. |

## 1.6 Other key issues: summary of the EAG's view

The EAG did not identify any other key issues.

## 1.7 Summary of EAG's preferred assumptions and resulting ICER

The incremental and total impact of the EAG's preferred assumptions are provided in Table 2 for probabilistic analyses.

**Table 2: Summary of EAG's preferred assumptions and ICER (deterministic)**

| Scenario | Incremental costs | Incremental QALYs*‡ | ICER (change from company base case) |
|---|---|---|---|
| Company's base case | [redacted] | 22.41* | [redacted] |
| Scenario 1. 3.5% discounting of both costs and effects (Key issue 6) | [redacted] | 17.57* | [redacted] (+ 27.54%) |
| Scenario 3. Include caregiver QALYs for ECM arm (Key issue 7) | [redacted] | 22.41* | [redacted] (± 0%) |
| Scenario 4. Change caregiver utility impact calculation (Key issue 7) | [redacted] | 9.03* | [redacted] (+ 148.3%) |

| Scenario | Incremental costs | Incremental QALYs*‡ | ICER (change from company base case) |
|---|---|---|---|
| Scenario 5. Changing the number of caregivers (Key issue 7) | [redacted] | 7.62* | [redacted] (+ 194.1%) |
| Scenario 6. Utilities and costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") (Key issue 8) | [redacted] | 22.97* | [redacted] (- 2.4%) |
| Scenario 7. Including givinostat monitoring costs | [redacted] | 22.41* | [redacted] (+1.06%) |
| Scenario 8. Including costs due to tertiary care and medical aids not captured in HERCULES | [redacted] | 22.41* | [redacted] (+ 2.48%) |
| Scenario 12. MAIC hazard ratio matched to CINRG DHNS on LOA applied to transition probabilities (Key issues 10 and 11) | [redacted] | 5.19* | [redacted] (+262.3%) |
| EAG's preferred base case + S1 + S3 + S4 + S5 + S6 + S7 + S8 + S12 | [redacted] | 0.27‡ | [redacted] (+6980%) |

**1.7x severity modifier applied to patient and carer incremental QALYs.*
*‡1.2x severity modifier applied to patient and carer incremental QALYs.*

The EAG did not identify or correct any relevant modelling errors (Section 5.3). For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.1.

# 2 INTRODUCTION AND BACKGROUND

This report provides a critique of the evidence submitted by the company, Italfarmaco, in support of givinostat for the treatment of treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older The following report considers the company evidence submission and executable model received by the EAG on 04/12/2024. It also considers the company's response to the EAG's clarification questions, which the EAG received on 24/01/2025.

## 2.1 Critique of the company's proposed place of the technology in the treatment pathway and intended positioning of the intervention.

Full details of the technology, its mechanisms of action, and the intended positioning of the intervention are described in section B.1 of the company submission (CS). The EAG consider the CS provides an accurate overview of the technology being appraised and of the health condition (CS, sections B.1.2 and B.1.3).

DMD is a rare genetic condition caused by mutations in the dystrophin gene, occurring almost exclusively in males. To date, only one treatment has been recommended by NICE for DMD. Ataluren was assessed under the Highly Specialised Technology route as HST22: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene.[2] EAG clinicians also observed that patients in the UK who met the criteria for ataluren would likely already be receiving the treatment. This was reflected in the treatment pathway figure submitted by the company (Figure 10, Section B.1.3.7 of the CS). In response to EAG clarification question A.10, the company confirmed that, although the combination of givinostat and ataluren has not been evaluated in clinical trials, the use of ataluren with givinostat is not contraindicated in the Summary of Product Characteristics (SPC) nor is it listed as a known interactions with givinostat.

The company's description of the proposed place of givinostat in the treatment pathway is considered appropriate by the EAG (Figure 10, Section B.1.3.7 of the CS). The CS describes treatment of DMD as multi-disciplinary and multi-component. EAG clinical advisors agreed that established clinical management (ECM) for neuro-muscular symptoms includes corticosteroids, physiotherapy and 'other' supportive care. Corticosteroids are the current pharmacological standard of care in the UK for treatment of neuromuscular symptoms in DMD. The CS cites a 2023 conference abstract[7] noting that 73% of DMD patients in the UK were taking a corticosteroid (CS, Section B.1.3.7). The CS states that givinostat is intended to be used alongside ECM and is not intended to displace corticosteroids. The EAG's clinical advisors considered the proposed positioning of givinostat appropriate.

EAG clinical advice agreed with the CS that the majority of newly diagnosed DMD patients in the UK would be started on corticosteroids and that the most commonly used in the UK is

prednisolone, followed by deflazacort. However, the EAG note that vamorolone (a modified corticosteroid with a more tolerable side effect profile) was recommended by NICE on 16/01/2025 for treating people with DMD who are aged 4 years and over (TA1031).[3] At the time of submission of the current appraisal (ID6323), vamorolone had not been approved by NICE and the CS does not explicitly consider the use of vamorolone as an alternative to prednisolone or deflazacort, as part of ECM. The EAG acknowledge that there is uncertainty about future use and market share of vamorolone. However, EAG clinical advice noted that newly diagnosed DMD patients may be more likely to choose vamorolone instead of standard corticosteroids. If real-world evidence from clinical practice aligns with the randomised trial evidence[8] in support of a lower risk of side effects with vamorolone, the EAG consider that vamorolone's market share will increase over time. However, there is uncertainty whether existing DMD patients would switch and may prefer to continue with their established corticosteroid regimen. The implications of vamorolone displacing current corticosteroids as part of ECM for DMD, were not considered in the CS.

**Key Issue 1: Have relevant comparators been specified in the submission?**

### 2.1.1 Marketing authorisation

At the time of the company's submission to NICE, their application for marketing authorisation in the UK was in process under the International Recognition procedure (with the Food and Drug Administration [FDA] as the reference regulator). Conditional marketing authorisation for givinostat for the treatment of DMD in patients 6 years and older with all genetic variants of DMD was approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) on 20 December 2024.[9] Although the MHRA endorsed the reference regulator's conclusions for ambulatory patients, they note that approval covered a wider indication including non-ambulatory patients (i.e., non-ambulant at start of treatment) for which there is, currently, no confirmatory evidence from clinical trials. As such, due to the wider indication considered by the reference regulator, the MHRA granted a conditional authorisation for givinostat, dependent on the outcome of the company's ongoing clinical trial in non-ambulatory patients (ULYSSES – NCT05933057).[10] Results are anticipated in October 2028.

## 2.2 Critique of company's definition of decision problem

**Table 3 summarises the decision problem as outlined in the NICE scope[11], how this was addressed in the company submission, and summarises the EAG's critique. The company's definition of the decision problem does not fully match the NICE scope. In particular, the EAG note that the population addressed by the CS is narrower and focuses on a subgroup of DMD patients who are ambulant when they initiate givinostat. The EAG's clinical advisors considered an ambulant population to be clinically appropriate. However, the EAG note that there are multiple measures and assessments to categorise ambulation status. A recent study suggests that the differences between ambulation measures and definitions for patients with DMD can impact the identification of ambulant vs non-ambulant patients.[12] The EAG is not**

**clear if a subgroup of ambulatory patients could be consistently identified in UK clinical practice.**

**Key Issue 2: Definition of 'ambulant' status and implications for UK clinical practice**

The NICE scope specifies two comparators of interest; established clinical management (ECM) without givinostat, and ataluren. The CS only includes ECM without givinostat as a comparator. The EAG is satisfied that the company's exclusion of ataluren is appropriate on the basis that ataluren is only indicated for boys with a premature stop codon DMD variant, which is a very small proportion of the overall DMD population. Givinostat is indicated across all DMD genetic variants. The CS puts forward two additional reasons for excluding ataluren as a comparator. These are noted in Table 3 along with the EAG's critique.

**The omission of ataluren is considered as a key issue and incorporated in Key Issue 1.**

The EAG also note that four of the 17 outcomes specified in the NICE scope were not included in the company submission. However, the EAG's clinical advisors were satisfied that the outcomes reported by the CS were appropriate. The company did not collect health-related quality of life data using EQ-5D, the preferred measure of health-related quality of life in adults in the NICE reference case. Only three of the outcomes specified in the scope are included the company's economic model: walking ability, lung function, adverse effects of treatment. However, this reflects the health states used in the company's preferred model (the HERCULES model) and the EAG considers that the submitted model is largely aligned with the scope.

**Table 3 Summary of decision problem: comparison of NICE scope and company submission**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| Population | People with Duchenne muscular dystrophy (DMD) 6 years of age and older | People with DMD 6 years of age and older who are ambulant when they initiate givinostat | The company states that the population in their decision problem aligns with the phase 3 EPIDYS trial for givinostat and is consistent with the available clinical data compared to current standard of care. They note that data for boys/ young men who initiate givinostat when non-ambulant are expected from the ULYSSES trial in late 2028. | The population addressed is narrower than the NICE scope, as it focuses on a subgroup of DMD patients who are ambulant when they initiate givinostat. The EAG's clinical advisors considered this was appropriate. However, the EAG are unsure how a subgroup of ambulatory patients will be consistently identified in UK clinical practice.<br><br>Although the CS focuses only on ambulant patients, the company has marketing authorisation for givinostat in both ambulant and non-ambulant patients. MHRA approved the conditional marketing authorisation of givinostat for the treatment of DMD in patients 6 years and older with all genetic variants of DMD on 20 December 2024.[9] This approval includes non-ambulatory patients, for which there is no evidence from clinical trials. As such, the MHRA granted a conditional authorisation for givinostat, dependent on the outcome of the company's ongoing ULYSSESS trial (NCT05933057) in non-ambulatory patients, due to complete in 2028. |
| Intervention | Givinostat | As per NICE scope | NA | The EAG has no concerns. |
| Comparator(s) | • Established clinical management without givinostat | • Established clinical management without givinostat | The company states that the European Medicines Agency recommended in June 2024 that the marketing | The EAG considers the exclusion of ataluren to be appropriate. Ataluren is only used for boys with a premature stop codon, which is a small subset of |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | • Ataluren (for people aged 2 years and older with a nonsense mutation in the dystrophin gene and can walk [ambulatory]) | | authorisation for ataluren should not be renewed, having concluded that the totality of the evidence shows a negative benefit-risk balance. The company considers that the use of ataluren as part of routine National Health Service (NHS) clinical practice for treatment of DMD may become uncertain during the course of the appraisal of givinostat.<br>The company also note that ataluren is only approved for a small subgroup of ambulatory patients who have a nonsense mutation in the dystrophin gene, which they say is approximately 10-15% of boys and young men with DMD. They say that as a result, ataluren was appraised by NICE using the highly specialised technology route, so ataluren was assessed against a different cost-effectiveness threshold, than the single technology appraisal route for givinostat. The company states that if an assessment of cost-effectiveness vs. ataluren is deemed to be necessary by NICE, then any appraisal should also be considered separately | those who have a point mutation. Therefore, ataluren would not be used for those with the majority of DMD genetic mutations. This was confirmed by the EAGs clinical advisors.<br><br>The company provides two further reasons for the exclusion of ataluren.<br>(i) The company suggests that use of ataluren for DMD may become uncertain, due to EMA recommendation that the marketing authorisation for ataluren should not be renewed. The EAG considers this to be reasonable but notes that there is no publicly available information to suggest that the MHRA plans to re-appraise ataluren.[13, 14]<br><br>(ii) That it is not appropriate to compare ataluren and givinostat because ataluren was considered under the Highly Specialised Technology process and givinostat is considered under the Single Technology process. Although the QALY threshold differs between the two processes, the EAG does not agree that this would preclude the company from including ataluren as a comparator in a de novo assessment of cost-effectiveness. Further, the EAG notes the CS also considers that givinostat should have been appraised via the HST route. |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | | | under the highly specialised technology route. | |
| Outcomes | • Walking ability (ambulation)<br>• Muscle function<br>• Muscle strength<br>• Ability to undertake activities of daily living<br>• Bone function<br>• Cardiac function<br>• Concordance and optimisation of treatment<br>• Endocrine function<br>• Lung function<br>• Time in wheelchair<br>• Number of falls<br>• Time to scoliosis<br>• Lower body function<br>• Upper body function<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life (people with DMD and carers). | • Walking ability (ambulation)<br>• Muscle function<br>• Muscle strength<br>• Ability to undertake activities of daily living<br>• Cardiac function<br>• Concordance and optimisation of treatment<br>• Lung function<br>• Time to scoliosis<br>• Lower body function<br>• Upper body function<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life (people with DMD and carers) | Outcomes relating to bone function, endocrine function, time in wheelchair, and number of falls are not included due to a lack of data. | Four of the 17 outcomes specified in the NICE scope were not included in the CS: bone function, endocrine function, time in wheelchair, number of falls. These outcomes were not pre-specified in the main clinical studies and no data were reported for these outcomes in the CS. Of these four outcomes, only endocrine function is recommended by the EMA. [redacted]Although the majority of outcomes are measured in the company's clinical studies only three inform the company's economic model: walking ability, lung function, adverse effects of treatment. However, the EAG considers that the submitted model is largely aligned with the scope. |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case (including discounting of costs and effects at 3.5%) stipulates that the time horizon for estimating clinical and cost effectiveness should be | Cost-utility analysis largely aligned with the NICE reference case except discounting effects at 1.5% beyond 30 years.<br><br>The cost-effectiveness of givinostat expressed in terms of the incremental cost per QALY gained over a lifetime | Company justifies Company justifies 1.5% discounting beyond 30 years with reference to DMD being a condition that severely impacts quality of life and givinostat having a long-term benefit, beyond discontinuation of givinostat, due to delayed LOA. | The EAG considers that the submitted model is largely aligned with the decided scope.<br><br>The EAG does not accept the use of 1.5% discounting of effects beyond 30 years as the reference case of 3.5% was followed in the recent ataluren and vamorolone NICE appraisals and in published models. There is also no |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective. | horizon from the perspective of the National Health Service (NHS) and Personal Social Services (PSS).<br><br>The submission utilises the CEM developed by Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis), led by Duchenne UK.<br><br>Health state occupancy is based on the published NHM and propensity score matching analyses. Utilities informed by the literature. Costs informed by UK-specific sources. | | evidence available on long-term benefit of givinostat beyond discontinuation and EAG clinical advice was that this long-term benefit is unknown. |
| Subgroups | No subgroups are identified in the NICE scope. | No subgroups are identified by the company in the decision problem | NA | NA |
| Special considerations including issues related to equity or equality | None highlighted in the NICE scope. | No special considerations are identified by the company in the decision problem | NA | NA |
| Other considerations | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that | NA | NA | NA |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | has underpinned the marketing authorisation granted by the regulator. | | | |

# 3 CLINICAL EFFECTIVENESS

## 3.1 Identification and selection of relevant studies for CS

The company submitted a systematic literature review (SLR) of clinical effectiveness which the EAG critiqued using the Risk of Bias in Systematic reviews (ROBIS) tool.[15] In clarification question C1, the EAG requested the protocol for the clinical effectiveness SLR.[16] The EAG consider that the review broadly adheres to established conduct guidance.

Although the SLR protocol included terms for identifying 'multinational or UK natural history studies' (clarification question C1), the CS does not provide sufficient detail for the EAG to assess the selection of studies to inform the unanchored indirect comparison (uITC). See section 3.4 for the EAG's critique of the CS uITC. The EAG's ROBIS critique is reported in APPENDICES
Appendix 1.

In clarification question C2, the EAG queried why the SLR searches had included ataluren but studies of ataluren were excluded from the CS. The company responded that the CS SLR was part of a global clinical review, with an additional stage to ensure identified evidence aligned with the NICE decision problem. As the company do not consider ataluren to be a relevant comparator, it was removed from the SLR at the alignment stage (despite it being listed as a comparator in the NICE scope) (**Key Issue 1** and Section 2.2). The EAG accept the company's response that the appropriate clinical studies were identified in the SLR.

## 3.2 Overview of clinical evidence reported in company submission

The clinical evidence included in the CS focuses on two company studies; EPIDYS (Study 48) and OLE (Study 51). The study name abbreviations will be used in the EAG report, rather than study numbers. EPIDYS is the pivotal trial for this submission and is a randomised, double-blind, placebo-controlled study. The EAG's critique is presented in section 3.3.1. OLE is an uncontrolled, non-randomised extension study to EPIDYS. However, OLE also enrolled participants from an additional company study (Study 43)[17] and participants who had not previously been enrolled in any company clinical study (but had met eligibility criteria for EPIDYS). The EAG's critique of OLE is presented in section 3.3.2.

The CS includes a uITC to estimate the effectiveness of givinostat relative to ECM over the longer-term, to inform estimates for the economic model. Data from EPIDYS and OLE were used to inform a givinostat 'arm' in the uITC and a UK-based registry study was used to inform ECM. The UK-based registry data was reported in a conference abstract detailing a retrospective case note review study.[18] The EAG critique the registry data and methods used in the uITC in Section 3.4.

## Table 4 Overview of studies and outcomes informing clinical effectiveness

| NICE scope category | Key outcomes | Recommended by EMA | Outcome | Treatment comparison | Source of data | Results reported in CS | Included in company model |
|---|---|---|---|---|---|---|---|
| Walking ability (ambulation) | Four-stair climb (4SC) | Yes | Primary | Direct, randomised (vs. placebo) | EPIDYS (Group A) | Yes | No |
| | | | Post hoc | Direct, randomised (vs. placebo) | EPIDYS (Overall) | Yes | |
| | | | Exploratory | NRS (delayed vs. givinostat) | OLE | Yes | |
| | Loss of ambulation | Yes | Secondary | Direct, randomised (vs. placebo) | EPIDYS | No[±] | No |
| | Age at loss of ambulation* | No | Post hoc | Direct, randomised (vs. placebo) | EPIDYS | No | No |
| | | | Secondary | Single arm (no comparator) | OLE | Yes | Partially[+] |
| | | | NA | Single arm | UK registry study | Yes[^] | Partially |
| | | | Exploratory | NRS (delayed vs. givinostat) | OLE | Yes | No |
| Lung function | Respiratory function (FEV1 (L), FVC (L), FEV1/FVC (%) and PEF (L/min)) | Yes | Secondary | Direct, randomised (vs. placebo) | EPIDYS | No | Partially[**] |
| | | | Secondary | Single arm (no comparator) | OLE | Yes | Partially[+] |
| | | | Exploratory | NRS (delayed vs. givinostat) | OLE | No | No |
| | Age at non-invasive ventilation* | No | Post hoc | Direct, randomised (vs. placebo) | EPIDYS | Yes | No |
| | | | Secondary | Single arm (no comparator) | OLE | Yes[^] | Partially[+] |
| | | | NA | Single arm | UK registry study | Yes | Partially |
| | | | Exploratory | NRS (delayed vs. givinostat) | OLE | No | No |
| | Age at FVC<1L* | No | Secondary | Single arm (no comparator) | OLE | Yes[^] | Partially[+] |
| | | | NA | Single arm | UK registry study | Yes | Partially |
| | | | Exploratory | NRS (delayed vs. givinostat) | OLE | No | No |
| | Age at FVC<30%* | No | Secondary | Single arm (no comparator) | OLE | No | No |
| | | | NA | Single arm | UK registry study | No | No |
| | | | Exploratory | NRS (delayed vs. givinostat) | OLE | No | No |
| Adverse effects of treatment | AEs and SAEs* | Yes | Secondary | Direct, randomised (vs. placebo) | EPIDYS | Yes | Yes |
| | | | Primary | Single arm (no comparator) | OLE | Yes | Yes |

*Described in CS as included in the economic model. **only givinostat arm, [+]only data from EPIDYS-givinostat and OLE naïve givinostat group used. ^Kaplan-Meier data not reported – estimates were calculated applying an acceleration factor derived from UK registry study. [±]reported in Mercuri et al (2024)[18].

## 3.3 Critique of the evidence of clinical effectiveness

Table 4 summarises the key company studies, data sources, outcomes and results informing the clinical effectiveness of givinostat, including outcomes and data considered in the uITC. The key outcomes listed in Table 4 include the primary outcomes from EPIDYS and OLE, and key secondary and exploratory outcomes for data sources that inform the economic model (including the UK registry study). The table maps key outcomes to the NICE scope, and those recommended by the European Medicines Agency (EMA) for clinical studies in DMD. Table 4 also describes the data sources informing each outcome, if results are reported in the CS, and if the results informed the economic model.

Table 5 summarises the study design, interventions, inclusion criteria, and outcomes for EPIDYS [19] and OLE [20] and Study 43.[17] The CS does not provide results for Study 43 and the EAG critique will focus on EPIDYS, OLE, and the uITC.

The EAG note that the estimates of treatment effect and safety used in the company economic model are not based on randomised comparisons from EPIDYS and are derived from a uITC and matching adjusted indirect comparison (MAIC). As such, it is potentially misleading to describe the EPIDYS RCT as the primary evidence base for the submission (CS Table 9). There are also minor discrepancies between CS Tables 9 and 11, with respect to the outcomes from EPIDYS that inform the economic model, which the EAG report discusses in section 3.3.1.4. The EAG agrees with CS Table 10, that results from the OLE study inform the economic model, but note that the treatment effects estimated via the uITC are age at loss of ambulation (LOA), age at forced vital capacity <1L (FVC<1L), and age at FVC<30% for a subgroup of OLE participants and not the whole cohort. Although both EPIDYS and OLE included health related-quality of life outcomes, they are not used in the company economic model submission (See sections 3.3.1.6, 3.3.2.5 and 4.2.7)

### 3.3.1 EPIDYS (Study 48)

#### *3.3.1.1 Study design*

EPIDYS is an 18-month, multi-centre, randomised, double-blind, placebo-controlled study, conducted in 41 tertiary care sites across 11 countries: UK, US, Canada, Belgium, France, Germany, Israel, Italy, the Netherlands, Serbia, and Spain.

Ambulant boys (n=179) with genetically confirmed DMD were randomised (using a 2:1 ratio) to receive oral givinostat (n=118) or placebo (n=61), in addition to ECM. Randomisation was stratified by the concomitant corticosteroid type (deflazacort/ other) and regimen (daily/ intermittent) given as part of ECM. This led to four strata (See Figure 1): deflazacort daily (givinostat: n=84; placebo: n=39), deflazacort intermittent (givinostat: n=7; placebo: n=6), other steroids daily (givinostat: n=15; placebo: n=9), and other steroids intermittent

## Table 5 Study details for EPIDYS and OLE, and Study 43

| | EPIDYS (Study 48) | OLE (Study 51) | Study 43 |
|---|---|---|---|
| **Design** | Multi-centre, randomised, double-blind, placebo-controlled phase 3 trial | Open label, multicentre long-term study in subjects with DMD who were previously treated in one of the givinostat studies, and subjects who were screened in EPIDYS, met all the inclusion criteria and none of the exclusion criteria and were not randomised because the enrolment in the off-target group was completed | Phase 1/2, proof of concept, open-label study |
| **Intervention** | Givinostat group (n=118)<br>Placebo group (n=61) | Givinostat group (n=119 at 31 dec 2023)<br>Delayed givinostat group (n=58 at 31 Dec 2023)<br>Naïve givinostat group (n=30 at 31 Dec 2023) | Givinostat group (n=20)<br>Part 1: dose was escalated from givinostat 25 mg bid to 50 mg bid and then reduced to 37.5 mg bid.<br>Part 2: givinostat 37.5 mg (could be reduced to 25 mg bid) |
| **Inclusion criteria** | Ambulant males aged ≥6 years old with genetically confirmed diagnosis of DMD | Boys/young men aged ≥6 years old with DMD | Male children aged 7 to <11 years with an immunohistochemical and molecular diagnosis of DMD |
| | Completed two 4SC assessments with a mean of ≤8 seconds (≤1 second variance) | Participated in Study 43 or EPIDYS (participants from ULYSSESS and STUDY 52 will be added in the future); **or** met all the inclusion for the EPIDYS overall population but were not randomised | Able to complete the two screening 6MWT with a minimal distance of at least 250 m each and results of these tests must be within ±30 m of each other |
| | Time-to-rise of at least 3 seconds but less than 10 seconds | | On a stable dose of systemic corticosteroids for at least 6 months |
| | Had received systemic corticosteroids for at least 6 months | | At least 6 months of data on the 6MWT (the "historical" 6MWT). From the moment of the walking test assessment(s), the child must not have received any compound that could potentially affect the test, with the exception of the stable steroid treatment |
| **Location** | UK, US, Canada, Belgium, France, Germany, Israel, Italy, the Netherlands, Serbia, Spain | As per EPIDYS trial | Italy |
| **Primary Outcomes** | Disease progression, as measured by the change in the results of the 4SC assessment between baseline and 72 weeks | Type, incidence, and severity of treatment-related and non-related AEs and SAEs throughout the study | Change in histology comparing the brachial biceps biopsies before and after ≥12 months of treatment with givinostat |

| | | | |
|---|---|---|---|
| **Secondary outcomes (described in CS)** | • Change from baseline after 18 months in NSAA total score<br>• NSAA cumulative loss of function<br>• Time to rise from floor<br>• Distance walked in 6 minutes<br>• Muscle strength evaluated by knee extension<br>• Muscle strength evaluated by elbow flexion measured by hand-held myometry<br>• Mean change in vastus lateralis muscle fat fraction | For ambulant boys:<br>• Change from baseline in physical function (measured by the 6MWT, NSAA and timed function tests)<br>• change from baseline in muscle strength (e.g. knee extension and elbow function), at week 48 and yearly until end of study<br>For non-ambulant boys/young men:<br>• changes from baseline in physical function measured by the Egen Klassifikation score<br>• patient/caregiver reports of daily living activities measured by the Barthel Index<br>• upper limb muscle strength measured by hand-held myometry<br>In both ambulant and non-ambulant boys/ young men:<br>• performance of upper limb<br>• motor function measures<br>• respiratory function<br>• quality of life<br>age at major disease milestones | • Change in 6MWT<br>• NSAA and performance of the upper limb test after treatment with givinostat<br>• Safety and tolerability (measured by AE collection, laboratory tests, physical examination, vital signs, ECG, echocardiogram and spirometry) |

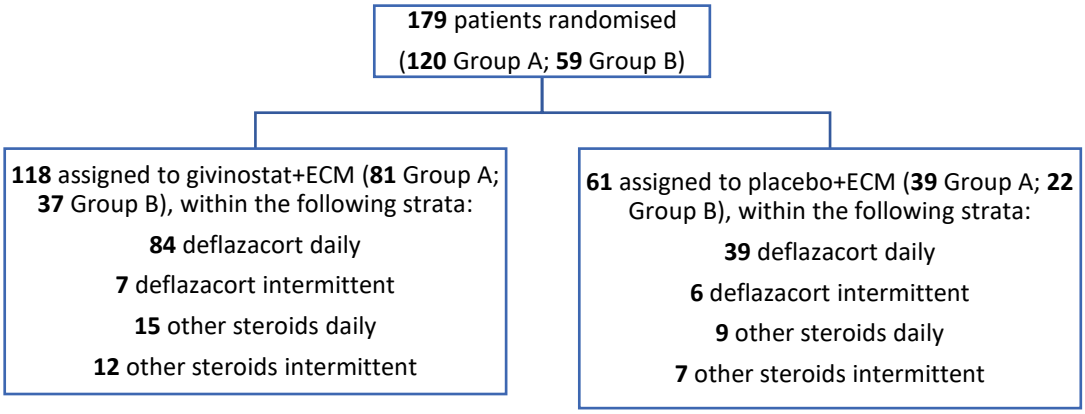
Abbreviations: DMD= Duchenne muscular dystrophy. 4SC= four stair climb. NSAA = North Star Ambulatory Assessment. 6MWT= 6-minute walking test. AE= adverse event. SAE= serious adverse event.

(givinostat: n=12; placebo n=7). Additionally, recruitment was pre-specified in two groups: the "target ITT population (Group A)" and "off-target ITT population (Group B)".

- **Group A** included boys with a baseline vastus lateralis fat fraction (VLFF) of >5% but ≤30% (n=120). This group was recruited to provide a sample of patients who were not at risk of a complete and sudden loss of ambulation, but who, if receiving placebo, would show decline over the study duration in the function, strength, and fat fraction endpoints being measured.
- **Group B** included boys with a VLFF of ≤5% or >30% (n=59). This group was recruited to allow for the evaluation of the safety of givinostat in a broader population.

Overall, the EAG considers the EPIDYS study design to be appropriate. However, further considerations regarding the four corticosteroid strata and Group A/ Group B stratification are discussed in section 0 (population), section 3.3.1.7 (risk of bias assessment), and section 3.3.1.4 (results).

**Figure 1 EPIDYS group assignment**




### *3.3.1.2 Population*

Eligible participants were ambulant boys aged ≥6 years with genetically confirmed DMD, who had a time-to-rise from floor (TTRFF) of ≥3 seconds but <10 seconds and had completed two 4SC assessments with a mean of ≤8 seconds (≤1 seconds variance). Further, eligible participants were required to have received stable systemic corticosteroids for at least 6 months prior to study entry and have an expectation that corticosteroid dose and regimen would not change over the duration of the study (CS Table 11).

The EAG notes that the study population differs from the decision problem specified by the NICE scope. The EAG also sought clarification regarding the definition of 'ambulant' used in EPIDYS (clarification question A2)[16]. The company responded that the criteria for defining boys as ambulatory were the mean of two screening 4SC assessments of ≤8 seconds (results of the two 4SC screening tests must have been within ±1 second of each other), and TTRFF of between ≥3 and <10 seconds at screening. The EAG's clinical advisors considered the assessment of ambulation within EPIDYS to be appropriate. However, they noted that choice of outcome measures may not reflect clinical practice in the UK, as the 6-minute walking test (6MWT) and 4SC would not usually be assessed in routine clinic visits (access to

the four stairs needed for completion of the 4SC might not be available in all settings). The North Star Ambulatory Assessment (NSAA)[21] would be more commonly used, in which those who cannot walk 10 meters independently (with no time limit) would be judged as non-ambulant. Although the EAG does not anticipate that this difference affects the validity of the trial results, it may have implications for the generalisability of findings. For example, a broader definition of ambulant might be used in practice and this would be in line with the conditional marketing approval for givinostat. The EAG considers the definition and measurement of 'ambulant' status in the CS and implications for generalisability to UK clinical practice as a Key Issue (**See Key Issue 2).**

Only 13 participants included in the EPIDYS trial were from the UK.[19] Clinical advisors noted that there would be a higher proportion of Asian patients seen in practice in the UK than were included in EPIDYS. The EAG notes that a 2017 longitudinal cohort study of children diagnosed with DMD in the UK between 2005 and 2014, which included data from 33 children of white British heritage and 23 of South Asian heritage, reported that children from South Asian background had earlier loss of ambulation and were more likely to decline or stop steroids.[22]

Baseline characteristics are reproduced in Table 6 (from CS, Table 17) for the 'overall' (Group A and B) and for Group A (target ITT) populations. Baseline characteristics appear balanced across the givinostat and placebo treatment groups. However, baseline data for Group B ('off-target' ITT population) were not reported in the CS and were requested by the EAG in clarification question A4.[16] In response, very limited baseline data were provided (see Table 6), for age, BMI, weight, time since diagnosis, time since corticosteroid initiation, and total NSAA score for the givinostat arm only. Due to these limited baseline data, the EAG are not able to comment on whether characteristics are balanced between the givinostat and placebo groups in Group B. The EAG also notes they are unable to comment on key baseline measures of ambulatory status or VLFF for either Group B or the overall EPIDYS population. To be eligible for Group B baseline VLFF needed to be $\leq$ 5% or >30%. However, in terms of disease progression, a VLFF of $\leq$ 5% is indicative of less degeneration in muscle function and a VLFF of >30% indicative of greater degeneration. The implications of this for the trial results are discussed in section 3.3.1.4.

The groups appear balanced within corticosteroid type (deflazacort, prednisone) and within steroid schedule (daily, intermittent). However, randomisation was stratified by both corticosteroid type and schedule, resulting in four strata (deflazacort daily regimen; deflazacort intermittent regimen; other steroids daily regimen; other steroids intermittent regimen). As baseline characteristics and measures are not reported by these strata, the EAG are not able to confirm if the arms are balanced across all four corticosteroid strata. (See section 3.3.1.3 for further critique of established clinical management).

## Table 6 EPIDYS patient baseline characteristics (modified from Table 17 of the CS)

| Characteristic | Overall population | | Group A population | | Group B population | |
|---|---|---|---|---|---|---|
| | Givinostat n=118 | Placebo n=61 | Givinostat n=81 | Placebo n=39 | Givinostat* n=37 | Placebo n=22 |
| **Age, years** | 9.8 (2.0) | 10.0 (2.1) | 9.6 (1.9) | 9.8 (2.1) | 10.1 (2.3) | NR |
| **Race** | | | | | | |
| **White** | 106 (90) | 57 (93) | 74 (91) | 36 (92) | NR | NR |
| **Asian** | 4 (3) | 2 (3) | 3 (4) | 1 (3) | NR | NR |
| **Black** | 3 (3) | 0 | 0 | 0 | NR | NR |
| **Other** | 5 (4) | 2 (3) | 4 (5) | 2 (5) | NR | NR |
| **BMI, kg/m$^2$** | 19.7 (4.10) | 19.9 (4.40) | 19.5 (3.83) | 20.1 (4.52) | 20.2 (4.6) | NR |
| **Weight, kg** | 31.2 (8.9) | 32.6 (10.8) | 30.2 (7.1) | 31.8 (9.6) | 33.5 (11.6) | NR |
| **Time since diagnosis, years** | 5.5 (2.6) | 5.6 (2.7) | 5.7 (2.5) | 5.6 (2.9) | 4.9 (2.7) | NR |
| **Dystrophin mutation** | | | | | | |
| **Deletion** | 83 (70) | 40 (66) | 58 (72) | 28 (72) | NR | NR |
| **Duplication** | 17 (14) | 14 (23) | 13 (16) | 9 (23) | NR | NR |
| **Point mutation** | 18 (15) | 7 (11) | 10 (12) | 2 (5) | NR | NR |
| **Time since corticosteroid initiation (years)** | | | | | | |
| | 3.6 (2.1) | 4.0 (2.1) | 3.7 (2.1) | 3.8 (2.1) | 3.4 (2.2) | NR |
| **Type of corticosteroid, n (%)** | | | | | | |
| **Prednisone** | 20 (16.9) | 15 (24.6) | 10 (12.3) | 10 (25.6) | NR | NR |
| **Deflazacort** | 91 (77.1) | 45 (73.8) | 66 (81.5) | 29 (74.4) | NR | NR |
| **Other** | 7 (5.9) | 1 (1.6) | 5 (6.2) | 0 | NR | NR |
| **Corticosteroid schedule, n (%)** | | | | | | |
| **Daily** | 99 (83.9) | 48 (78.7) | 69 (85.2) | 31 (79.5) | NR | NR |
| **Intermittent** | 19 (16.1) | 13 (21.3) | 12 (14.8) | 8 (20.9) | NR | NR |
| **Additional baseline clinical characteristics*** | | | | | | |
| **Total NSAA score (mean [SD])** | NR | NR | 24.44 [5.09] | 24.67 [4.79] | [redacted] | NR |
| **Time to rise, seconds (mean [SD])** | NR | NR | 5.57 [1.86] | 5.59 [1.96] | NR | NR |
| **Time to run/walk 10 metres, seconds (mean [SD])** | NR | NR | 5.41 [1.24] | 5.18 [0.95] | NR | NR |
| **Distance walked in 6 minutes, metres (mean [SD])** | NR | NR | 403.31 [72.11] | 399.64 [63.83] | NR | NR |
| **VL MFF assessed by MRS, % (mean [SD])** | NR | NR | 15.45 [6.37] (n=77) | 15.95 [6.66] (n=37) | NR | NR |
| **VL MFF assessed by MRS, % (median [IQR; Q1, Q3])** | NR | NR | 15.00 [10.00, 21.00] (n=77) | 15.00 [10.00, 20.00] (n=37) | NR | NR |

Source: Table 17 of the CS; *company response to clarification question A4.
Data are median (IQR), n (%), or mean (SD); range. Abbreviations: BMI, body mass index; IQR, interquartile range; ITT, intention-to-treat; MRS, magnetic resonance spectroscopy; n, number; SD, standard deviation; NR, not reported.

#### *3.3.1.3 Interventions*

The interventions used in EPIDYS are outlined in the CS in Table 11. Participants in the intervention group received oral givinostat (10mg/ml), twice daily after a meal, in combination with ECM, including standard corticosteroid therapy. The placebo group, received placebo (10mg/ml), twice daily after a meal, in combination with ECM including standard corticosteroid therapy.

A flexible treatment regimen was used, with starting dose chosen according to body weight, (Appendix M.2 of the CS). The weight-based starting dose of oral givinostat was 20–70mg twice a day, with a reduced dose of 13–47mg twice a day. Dose reductions were prespecified if adverse events occurred or if boys lost weight during the study. In June 2018, a safety review of haematological data led to a protocol amendment which reduced the starting dose to 13–47 mg twice a day, with a reduced dose of 11–37 mg twice a day. In response to clarification question A6, the company provided the proportion of participants recruited pre- and post- protocol amendment.[16] The groups were small (pre-change n=58, post change n=62) but reasonably balanced and, coupled with the CS subgroup analyses, the EAG agrees that there is no evidence to suggest dose regimen modified treatment effect (see EAG report section 3.3.1.4.1).

##### 3.3.1.3.1 Established clinical management

Both the givinostat and placebo arms of the EPIDYS trial included ECM, however the CS does not report the definition of ECM used in EPIDYS. The company's response to EAG clarification question A11[16] notes that the ECM criteria used in EPIDYS were to ensure that the givinostat outcomes were not confounded by other therapies. As such, the company note that their definition of ECM was based on the study the study inclusion criteria, exclusion criteria and concomitant medicine criteria, outlined in Table 11 of the CS, and the CS Appendix M1.1 and M.1.2. The EAG's clinical advisors considered ECM in the EPIDYS trial to be broadly similar to that used in UK clinical practice. The similarity of the ECM criteria used in EPIDYS compared to UK clinical practice is discussed further in section 3.4.2 of the EAG report with regard to sources of data used for the uITC.

Corticosteroids are the current pharmacological standard of care for DMD, as per the International DMD Care Considerations guidelines.[23] The inclusion criteria for EPIDYS stated that participants should have stabilised on systemic corticosteroids (for at least six months before givinostat treatment, with an expectation that dose/ regimen would not change during the study). The majority of participants included in EPIDYS were taking the corticosteroid deflazacort (givinostat 77.1%, placebo 73.8%) rather than prednisone (givinostat 16.9%, placebo 24.6%). The EAG note there is conflicting evidence in the wider literature regarding whether the effect of prednisone and deflazacort differ significantly.[24, 25] However, the EAG's clinical advisors considered that prednisolone is more commonly used in the UK and this is supported by longitudinal registry data reported in the CS (Section B.1.3.7). Citing a 2023 conference abstract, the CS notes that, between 2012-2022, 544 out of 800 UK patients (68%) who were prescribed a corticosteroid were taking prednisolone on

at least one observation recorded in the registry. Of these, 96.6% followed a daily, rather than intermittent, dose regimen.[7] The proportion of participants in EPIDYS with a daily corticosteroid schedule was lower (givinostat 83.9%, placebo 78.7%). Although the EAG do not anticipate these differences impact the validity of the EPIDYS results, it may raise questions about the generalisability of the findings to a UK context and has implications for the choice of appropriate data sources for the uITC (see section 3.4).

#### *3.3.1.4 EPIDYS Efficacy Results*

As pre-specified in the EPIDYS trial protocol (p.95),[26] primary efficacy analyses were planned for the Group A population only. Analyses for the overall population (which includes Group A and Group B participants) were conducted for 'supportive' analyses only. However, the EAG note that the population of interest in the CS economic model is the overall population (i.e. Group A and Group B combined). The results of the efficacy analyses in the Group A population are presented in section B.2.6 of the CS and are briefly noted below.

The primary outcome in EPIDYS was the 4SC and key secondary effectiveness outcomes were total NSAA score, NSAA cumulative loss of function, TTRFF, 6MWT, knee extension, elbow flexion and MRS VLFF. In the comparison of the results of 4SC between 18 months and baseline, the geometric least squares mean ratio was 1.27 (95% CI 1.17 to 1.37) in the givinostat group and 1.48 (1.32 to 1.66) in the placebo group (ratio 0.86, 95% CI 0.75 to 0.99; p=0.035) (see Table 7). This suggests that givinostat is more effective than placebo at reducing disease progression when measured by 4SC in the Group A population. The CS reports a post hoc analysis for the overall population (Group A and B combined) generalised least squares mean ratio =0.84 ((95% CI 0.73 to 0.96); p=0.0116). The EAG notes that, although it is the overall population that is of interest in the CS uITC and economic model (not Group A), 4SC is not an outcome of interest. The CS notes that the smaller decline in 4SC, attributable to givinostat, is of a magnitude considered clinically meaningful to patients with DMD, due to the nature of the disease. EAG clinical advice was supportive and noted that DMD is a progressive disease, in which small incremental improvements in outcomes were important to patients and made a meaningful difference.

Key secondary ambulation outcomes for Group A did not differ between groups after multiplicity adjustment using the Hochberg procedure (Figure 2 in the primary trial publication and Figure 17 in the CS).[19] The EAG consider this an appropriate adjustment. In section B.2.6.2, the CS stresses that givinostat was nevertheless 'numerically superior' to placebo for NSAA total score, cumulative loss of function, and TTRFF. Results for the overall population are reported in CS Figure 25 and reproduced in EAG Table 8. Although the direction of adjusted effects for key secondary outcomes may suggest a benefit of givinostat relative to placebo, the EAG raises concerns about the generalisability of these results to UK clinical practice. This is due to observed variation in results across the five separate functional outcome measures, variation between Group A and the 'overall' population, and differences between the measurement of ambulation within EPIDYS and UK clinical practice (see section 3.3.1.2).

The EAG notes a minor discrepancy between the outcomes listed in Tables 9 and 11 of the CS. In CS Table 9, the CS states that two EPIDYS endpoints, age at loss of ambulation and adverse effects of treatment, feed into the economic model. Whereas, in CS Table 11 the company state that age at loss of ambulation (LOA), and treatment-related adverse effects inform the model. Whilst lung function and treatment-related adverse effects were pre-specified outcomes in the EPIDYS trial protocol, age at LOA was not a pre-specified outcome, was not directly measured in EPIDYS and no results from EPIDYS for age at LOA are reported in the CS or main journal publication. However, results are reported for an exploratory endpoint pre-specified in the EPIDYS protocol named "proportion of subjects that lose ambulation during the study". The main EPIDYS trial publication reports that "*one boy, who was receiving placebo, lost ambulation at week 60*".[19] For completeness, the EAG report includes both age at LOA and LOA in Table 7 and in the risk of bias assessment in section 3.3.1.7. However, as this event occurred in the placebo arm of EPIDYS, it does not directly inform the CS economic model which is based on effects estimated via a uITC, informed by the givinostat arm of EPIDYS (See section 3.4 for details on the uITC).

Results for lung function outcomes are not presented in the clinical effectiveness section of the CS or within published trial reports. In reference to the uITC analyses in section B.2.8.4 of the CS, it is stated that "*As with age at NIV, there were zero events for FVC<1L amongst the patients receiving givinostat during the EPIDYS study follow-up*" (CS, p.110).

**Table 7: EPIDYS results for the primary outcome and the secondary outcomes that inform the company economic model**

| Outcome | Outcome category | Comparison | Analysis population | Result | EAG comments | Company risk of bias assessment | EAG risk of bias assessment* |
|---|---|---|---|---|---|---|---|
| **Primary outcome from EPIDYS** | | | | | | | |
| **Four-stair climb (4SC)** | Primary outcome | Givinostat + ECM vs. placebo + ECM | Group A | In the comparison between 18 months and baseline, the geometric least squares mean ratio was 1.27 (95% CI 1.17–1.37) in the givinostat group and 1.48 (1.32–1.66) in the placebo group (ratio 0.86, 95% CI 0.745–0.989; p=0.035) | Results for this outcome are presented in the Group A population and not for the overall population (CS section B.2.6.1). This outcome is prespecified in the EPIDYS trial protocol. This outcome does not inform the company economic model | Low | Some concerns |
| **Outcomes stated by the company to inform the economic model** | | | | | | | |
| **Age at loss of ambulation during the study** | Unclear | Givinostat + ECM vs. placebo + ECM | Unclear | Not reported within the clinical effectiveness section of the CS or published reports | The company state in the CS (Table 11) that "age at loss of ambulation during the study" informs the economic model. The EAG notes that this outcome is not pre-specified within the EPIDYS trial protocol, information (i.e. analyses/ results) for this outcome are not reported within the clinical effectiveness section of the CS or published reports, and only data for the givinostat group are used in the model | Not assessed | High |
| **Loss of ambulation** | Exploratory endpoint | Givinostat + ECM vs. placebo + ECM | Group A | Not reported within the clinical effectiveness section of the CS. The main journal publication states that "One boy, who was receiving placebo, lost ambulation at week 60." [19] | The company conducted a risk of bias assessment for "loss of ambulation" in response to the EAG's clarification question C6 - they stated that this outcome informs the indirect treatment comparison. The EAG notes that this outcome maps to the pre-specified outcome "proportion of subjects to lose | Low | Some concerns |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | ambulation during the study". However, data for this outcome are not reported within the clinical effectiveness section of the CS (but result is reported in main journal article for trial) | | |
| **Adverse effects of treatment** | Safety outcome | Givinostat + ECM vs. placebo + ECM | Safety population | Treatment-related adverse events occurred in 81 (69%) of the givinostat group and 17 (28%) of the placebo group. The company stated these are typically known to be related to givinostat treatment, including diarrhoea, thrombocytopaenia, and hypertriglyceridaemia | This outcome partially informs the economic model, as only data for the givinostat group in EPIDYS are used. Analyses conducted in the safety population but as all patients received at least one dose of the study drug, all patients were included. | Not assessed | Low |
| **Lung function** | Safety outcome (categorisation taken from EPIDYS trial protocol, as data are not reported in CS) | Givinostat + ECM vs. placebo + ECM | Safety population | Not reported within the clinical effectiveness section of the CS | Respiratory function was a pre-specified outcome in the EPIDYS trial protocol, but no information (i.e. analyses/ results) for this outcome is reported within the clinical effectiveness section of the CS. | Not assessed | High |

*The EAG's detailed risk of bias assessment, including rationale for judgements, is presented in section 3.3.1.7 and Appendix 2.

**Table 8 Key secondary ambulation outcomes from EPIDYS at 18 months (reproduced from CS Figure 17 and 25)**

| Endpoint | Group A ('Target ITT') | 'Overall' (Group A and B combined) |
|---|---|---|
| 4SC+ | 0.86 (0.75 to 0.99) | 0.84 (0.73 to 0.96) |
| NSAA total score+ | 1.91 (0.30 to 3.53) | 1.50 (0.11, 2.89) |
| NSAA total score (adjusted 95% CI)* | (-0.28 to 4.11) | NR |
| Cumulative loss of function+ | 0.61 (0.41 to 0.93) | 0.78 (0.56 to 1.11) |
| Cumulative loss of function (adjusted 95% CI)* | (0.35 to 1.08) | NR |
| Time to rise, sec+ | -3.28 (-9.57 to 3.02) | -3.64 (-9.50 to 2.22) |
| Time to rise, sec (adjusted 95% CI)* | (-10.50 to 3.94) | NR |
| 6MWT, m+ | 10.0 (-12.1 to 32.0) | 13.86 (-7.35 to 35.08) |
| 6MWT, m (adjusted 95% CI)* | (-12.07 to 31.98) | NR |

Treatment effects (difference in mean change from baseline) and 95% confidence intervals for givinostat vs placebo. Adjusted* and unadjusted+ estimates. Adjusted estimates reported following the Hochberg procedure for multiplicity and reproduced from Table 36 of the CSR. Number analysed are 118 for givinostat and 61 for placebo, Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walking test; CS, corticosteroids; NSAA, North Star Ambulatory Assessment; NR, not reported

#### 3.3.1.4.1 Subgroup analyses

Two pre-specified subgroup analyses are presented in section B.2.6.5 of the CS. Both are conducted for the primary outcome (4SC) and only in the Group A population ('target'). The subgroups are starting dose (due to protocol amendment, see section 3.3.1.3) and age at first dose (6-7 years; >7 years). The CS results suggest no evidence that the dosing regimen or age at first dose change modified treatment effects (CS, Figure 26). However, subgroup analyses were not reported for the overall EPIDYS population. The EAG note that it is the overall EPIDYS population (Group A and B) that informs the uITC and economic model in the CS and this overall group are representative of ambulatory patients seen in clinical practice.

The focus of EPIDYS was the Group A population. In response to clarification question A4 and A8, the company provided Group B data for 4SC only. At baseline, 4SC mean (SD) time was reported at 3.9 (1.4) seconds in the givinostat group (n=37) and 3.7 (1.6) seconds in the placebo group (n=22) of Group B, compared with 3.4 (1.1) and 3.5 (1.3) seconds in Group A. At 18 months (end of study), 4SC in Group B was 6.6 (7.9) in the givinostat group and 9.8 (13.3) seconds in the placebo group. This compared with 4.7 (3.2) and 6.4 (7.7) seconds in Group A. In response to clarification question A8, the company state that baseline 4SC was nominally higher in Group B. They note the 4SC results favoured givinostat and were consistent with the results for the Group A and overall ITT populations. The EAG considers the 4SC results for Group B to be consistent with the results for Group A in favouring

givinostat, although baseline 4SC was higher in Group B, suggesting a more advanced disease in this group. The company conducted a post-hoc analysis in the overall population for the primary and key secondary outcomes and report results were consistent results with those seen in Group A (CS, section B.2.6.4). However, results are not reported in the CS. The company reported that no secondary outcome data are available for Group B. As the population of interest in the economic model is the overall population (Group A and B), and the uITC includes an additional group of 30 participants equivalent to Group B, the EAG would have preferred to have been able to assess the EPIDYS Group A population and Group B population separately. The EAG cannot provide further critique.

#### *3.3.1.5 Safety results*

Adverse events (AEs) are summarised in CS section B.2.9.1 for the safety population (all randomly assigned patients who received at least one dose of the study drug). The EAG note that all patients had at least one dose of the study drug. Treatment-related adverse events (TRAEs) occurred in 81 (69%) of the givinostat group and 17 (28%) of the placebo group (Table 7). The company stated these are typically known to be related to givinostat treatment, including diarrhoea, thrombocytopaenia, and hyper-triglyceridaemia.

Severe adverse events (SAEs) occurred in 8 (7%) patients in the givinostat group and 2 (3%) patients in the placebo group. The only severe AE in two or more boys was vomiting. No patients died during the study. AEs occurred in 112 (95%) givinostat patients and 57 (93%) placebo patients. In the givinostat group, the most common AEs were diarrhoea and vomiting (in more than twice as many boys as placebo), nasopharyngitis, headache, decreased platelet count or thrombocytopaenia, increased triglycerides, and abdominal pain. AEs leading to withdrawal occurred in three (3%) patients in the givinostat group and none in the placebo group. AEs leading to dose reduction occurred in 42 patients (36%) in the givinostat group and 1 (2%) patient in the placebo group.

#### *3.3.1.6 Health-related quality of life*

Health-related quality of life (HRQoL) results are reported in section B.2.6.3 of the CS, for the Group A population only. The company did not collect health-related quality of life data using EQ-5D, the preferred measure of health-related quality of life in adults in the NICE reference case, but using the Pediatric Outcomes Data Collection Instrument (PODCI). There was no evidence to suggest HRQoL differed between the two arms at end of treatment (18 months). The difference in means (givinostat-placebo) of standardised global function scale scores from the PODCI was 2.96 (95% CI −1.41, 7.33; p=0.1824). However, the EAG note that the PODCI results do not inform the economic model, with the company preferring utilities sourced from external observational sources. In clarification question B11 the EAG sought to explore related to HRQoL the EAG suggested mapping of PODCI to EQ-5D by Posner et al. 2024[54] (See section 4.2.7 of EAG report).

#### *3.3.1.7 Protocol deviations*

Protocol deviations are reported in section 10.2 of the EPIDYS CSR. The EAG notes that the CSR focuses on major protocol deviations and that minor protocol deviations are listed in Table 16.2.3.2. Minor protocol deviations are not summarised here, as the EAG did not have access to this table.

In the overall population, 38 major protocol deviations were reported, in 20 patients (16.9%) and 12 patients (19.7%), in the givinostat and placebo groups, respectively. These were most commonly related to COVID-19. Six participants (four givinostat and two placebo) missed assessments and eight (four each group) had delayed assessments all due to COVID-19. A post-hoc subgroup analysis compared 4SC data for participants who completed the 72-week assessment outside of the specified window. The company reported that the trial was not modified as a result of the pandemic and an analysis of 4SC data that excluded boys who completed the 72week assessment outside of the specified window showed similar results to the main analysis (givinostat-to-placebo ratio 0.83 [0.70 to 0.99]).

The next most common category were "other" deviations. This included mis-randomisation in Group A/ Group B populations in six patients (four givinostat and two placebo, respectively), wrong stratification based on steroid regimen in three patients (one givinostat and two placebo, respectively), and invalidated functional test in two patients (one patient in each group). Two patients in the givinostat group had major protocol deviations which were related to "eligibility criteria not met" – both were due to a change of steroid treatment before the start of the study drug. Of these two patients, one subject was in Group A and one was not. No further information is reported on this. The EAG does not have concerns about these deviations and missing data are further considered within the risk of bias assessment presented in section 3.3.1.8.

#### *3.3.1.8 Risk of bias assessment (RoB 2)*

In the CS Appendix D.2.2.1, the company assessed risk of bias for EPIDYS at the trial-level, using the tool from Centre for Reviews and Dissemination (CRD) guidance for systematic reviews.[27] The company's assessment did not highlight any concerns with the trial. Although the approach taken by the company meets NICE requirements,[28] the EAG consider the Risk of Bias 2 (RoB 2) tool to be a more appropriate and robust tool for the assessment of risk of bias in randomised controlled trials, as it facilitates assessment at the outcome-level.[29] The EAG raised this with the company in clarification question C6 and the company provided a RoB 2 assessment for 4SC (the primary endpoint) and LOA. The company judged both outcomes to be at an overall low risk of bias. In clarification response A6, the company note that LOA was assessed as it is the endpoint used in the uITC. However, the EAG note that the LOA evidence informing the uITC (and economic model) does not arise from a randomised comparison and, as such, the assessment of risk of bias in the uITC for LOA should be considered separately (See section 3.4.5).

**Table 9 Risk of bias in key outcomes in the EPIDYS trial, assessed using RoB 2**

| EAG assessment | | | | | | | | Company assessment | |
|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | **Domain judgement** | | | | | | **EAG Rationale for overall judgment** | **Overall judgment** | **Rationale for overall judgement** |
| | **1** | **2** | **3** | **4** | **5** | **Overall** | | | |
| **Four stair climb** | Low | Low | Low | Low | Some concerns | **Some concerns** | Efficacy analyses only presented for Group A in CS. Although pre-planned in the protocol for the trial, in the CS all data are not presented separately for Group A, Group B, and the overall population, making it difficult to judge the selection of the reported result. The EAG asked for these data in clarification question A4 and A8 but the company did not provide it in full. | Low | Not provided<br><br>(all domains rated low risk) |
| **Loss of ambulation** | Low | Low | Low | Low | Some concerns | **Some concerns** | As above rationale for "some concerns" judgement. Additionally, the EAG notes there is limited information (i.e. analyses; results) reported for this outcome in the CS , though the main journal publication reports the following result: "One boy, who was receiving placebo, lost ambulation at week 60." [19] | Low | Not provided<br><br>(all domains rated low risk) |
| **Age at loss of ambulation** | Low | High | High | Some concerns | Some concerns | **High** | No information (i.e. analyses; results) for this outcome reported in the CS; outcome not pre-specified in trial protocol | Not assessed | N/A |
| **AEs of treatment** | Low | Low | Low | Low | Low | **Low** | No concerns | Not assessed | N/A |
| **Lung function** | Low | High | High | Low | Some concerns | **High** | No information (i.e. analyses; results) for this outcome reported in the CS | Not assessed | N/A |

Domains: 1: Randomisation process; 2: deviation from intended intervention; 3: missing outcome data; 4: measurement of the outcome; 5: selective outcome reporting. AEs = adverse events.

The EAG's RoB 2 summary assessment is reported in Table 9 (and presented in full in the Appendix, section 9.3). The EAG used the CS, the published trial report and the associated trial protocol to complete the RoB 2 assessment.[19] In addition to the two outcomes included in the company's assessment, the EAG also assess RoB for lung function, AEs and age at LOA. Although these outcomes do not directly inform the economic analysis, EPIDYS participants feed into the OLE, which in turn assesses AEs and 'age at major disease milestones' outcomes which in turn inform the economic analysis via the uITC. The EAG judges 4SC and LOA to be at some concerns for risk of bias, and age at LOA and lung function to be at high risk of bias. The EAG has no concerns for AEs, which were rated at low risk of bias.

### 3.3.2 OLE (Study 51)

#### *3.3.2.1 Study design*

Study 51 is an ongoing, open label extension study (OLE). It is a multi-centre, uncontrolled and non-randomised study examining the safety, tolerability, and efficacy of givinostat (NCT03373968). OLE recruitment commenced in October 2017 and results reported in the CS (Doc B section B.2.6.6) are based on a data cut-off date of 31/12/2023. 207 participants are currently enrolled and were previously enrolled in EPIDYS or an additional company study (Study 43).[30] Study 43 (NCT01761292) was a phase 1/2 open-label study to evaluate givinostat safety, tolerability, pharmaco-kinetics and effects on histology and clinical parameters. It completed in November 2017 and enrolled 20 participants. OLE also includes 30 participants who had not previously been enrolled in any company clinical study (but who had met eligibility criteria for EPIDYS – see section 3.3.2.2. In clarification question A7, the company confirmed participant flow across studies informing the CS. Figure 2 presents the EAG's summary of participant flow

#### *3.3.2.2 Population*

Participants were eligible for inclusion if they were aged 6 years or older, had participated in either Study 43 or EPIDYS, and had attended the end of study visit. Both Group A and Group B from EPIDYS were eligible. The third group of patients eligible for OLE were those who had been screened for participation in EPIDYS and had:

- Met all the inclusion criteria and none of the exclusion criteria,
- A baseline VL MFF assessed by MRS in the range $\leq$ 5% or >30%, i.e. included in 'off-target' group, and
- Were never randomised because the enrolment in the 'off-target' group (Group B) was completed.

The CS classifies participants by their previous exposure to givinostat at entry to OLE. This gives three groups: (i) a 'givinostat' group, who had previously received givinostat in either EPIDYS or Study 43, (ii) a 'delayed givinostat' group, who had been randomised to placebo in EPIDYS and (iii) a 'naïve givinostat' group, who had been screened and met criteria for EPIDYS, but had not been enrolled.

**Figure 2 Diagram of participant flow through the studies and data sources used in the CS**

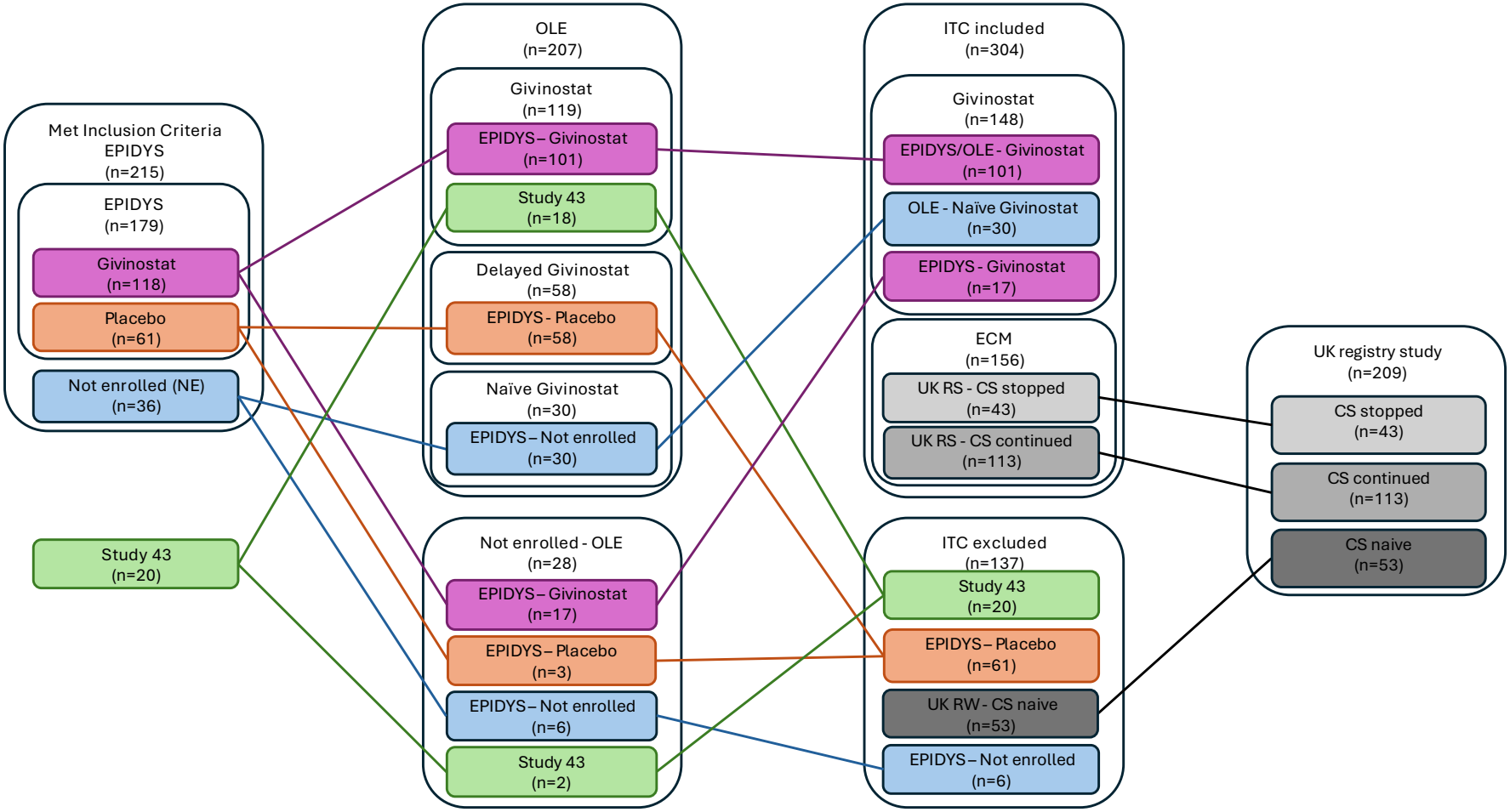



Figure depicts flow of participants through company studies (Study 43-Phase 1/2, EPIDYS-RCT, OLE-single arm) and how the company studies inform the unanchored indirect treatment comparison (uITC) submitted by the company for the current appraisal. The data used from the UK registry study for the uITC is also shown. N= number of participants.

The CS includes OLE findings from 207 participants. The givinostat group includes 119 participants (EPIDYS: n=101 and Study 43: n=18), the delayed group includes n=58 participants and naïve group includes n=30 participants.

Study 43 and EPIDYS had different inclusion criteria and a slightly different treatment regimen (see Table 5). Available baseline data is limited but, compared to the givinostat arm of EPIDYS Group A, Study 43 participants were slightly younger (mean: EPIDYS: 9.6 years; Study 43: 8.2 years), and disease was less progressed for mean 6MWT (EPIDYS: 403.3 metres; Study 43: 458.0 metres), mean NSAA total score (EPIDYS: 24.4; Study 43: 28.1), and mean time to rise (EPIDYS: 5.57 seconds, Study 43: 4.43 seconds).[17] Although the EAG is unable to provide a formal assessment, total givinostat exposure time is also likely to vary within the givinostat group, by participant study of origin (i.e. Study 43 started in 2013 and EPIDYS in 2017). The CS states that maximum givinostat exposure in OLE was 6.1 years. However, the CS further notes that 16 patients had been previously treated for up to 4 years with a maximum total exposure time of 10.1 years (CS, Section B.2.3.5).

The definition of non-ambulant in OLE is a patient who is unable to complete the 10 metre walk/run in 30 seconds or less without any support or devices (Clarification response A3). The EAG notes this definition appears to fit with the description of the Early Non-Ambulatory phase given in the CS (section B.1.3.3, Table 3) but the company were reluctant to confirm mappings between study measures of ambulatory status and stages of DMD (clarification response A3). The stages of DMD inform the health states used in the company's model (EAG section 4.2.2). The EAG note the definition of non-ambulant in OLE differs from that used in EPIDYS, which was based on 4SC (Section 3.3.1.2). **(Key Issue 2 and Key Issue 3).**

Nine participants in the OLE givinostat group, 3 in the 'delayed' givinostat group and zero participants in the 'naïve' group were non-ambulant at OLE baseline. The CS does not provide the breakdown by study origin (EPIDYS or Study 43) for the givinostat group. The EAG notes that, as data from OLE informs the givinostat 'arm' in the uITC and MAIC and that ambulatory status is a key health state in the economic model, ambulatory status at entry to OLE (by study of origin) is a potential source of selection bias that is not explicitly covered in the CS. Further, the EAG note a lack of clarity regarding the number of participants who are non-ambulant in the 'delayed' arm of givinostat at OLE baseline. The delayed group are those who were randomised to placebo in EPIDYS, and for which only one 'non-ambulant' event is reported at the end of the EPIDYS study period (See EPIDYS results, section 3.3.1.4). In section B.2.6.7 of the CS (p.95), the company note that 2 patients had become non-ambulant whilst receiving placebo. At OLE baseline, there are three non-ambulant participants. The EAG is unsure if this discrepancy may be related to the different definitions and measures of ambulation used across the company's studies.

## Table 10: OLE study: Patient baseline demographics and disease characteristics (abridged & reproduced from CS Table 20, CSR tables 15, 16, 18, 20, 22)

| Characteristic | Givinostat group N=119 | Delayed givinostat group N=58 | Naïve givinostat group N=30 | Overall N=207 |
|---|---|---|---|---|
| **Previous givinostat study, n** | | | | |
| **EPIDYS** | 101 | 58 | 0 | 159 |
| **Study 43** | 18 | 0 | 0 | 18 |
| **Screened for EPIDYS but not enrolled** | 0 | 0 | 30 | 30 |
| **Age, years** | 11.7 (2.1) | 11.5 (2.1) | 10.5 (2.3) | 11.5 (2.1) |
| **BMI at screening, kg/m$^2$** | 20.9 (5.0) | 21.3 (5.2) | 20.2 (4.0) | 20.9 (5.0) |
| **Weight at screening, kg** | 35.7 (10.9) | 37.3 (12.1) | 32.4 (9.6) | 35.7 (11.1) |
| **Ambulant status at screening, n (%)** | | | | |
| **Ambulant** | 110 (92.4) | 55 (94.8) | 30 (100.0) | 195 (94.2) |
| **Non-ambulant** | 9 (7.6) | 3 (5.2) | 0 | 12 (5.8) |
| **Time since diagnosis, years** | 7.6 (2.5) | 7.3 (2.7) | 6.9 (2.7) | 7.4 (2.6) |
| **Time since corticosteroid initiation (years)** | 5.7 (2.4) | 5.4 (2.3) | 4.5 (2.7) | 5.4 (2.4) |
| **Type of corticosteroid, n (%)** | | | | |
| **Prednisone** | 16 (13.4) | 15 (25.9) | 3 (10.0) | 34 (16.4) |
| **Deflazacort** | 99 (83.2) | 42 (72.4) | 27 (90.0) | 168 (81.2) |
| **Other** | 4 (3.4) | 1 (1.7) | 0 | 5 (2.4) |
| **Corticosteroid schedule, n (%)** | | | | |
| **Daily** | 93 (78.2) | 45 (77.6) | 28 (93.3) | 166 (80.2) |
| **Intermittent** | 26 (21.8) | 13 (22.4) | 2 (6.7) | 41 (19.8) |
| **Additional baseline clinical characteristics in ambulatory patients** | **Givinostat group N=110** | **Delayed givinostat group N= 55** | **Naïve givinostat group N=30** | **Overall N=195** |
| **6-minute walking distance (6MWT) (metres), Mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **NSAA score, mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **4-Stair Climb (4SC) (Seconds), Mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Time to walk 10 meters (Seconds), Mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Time to rise from floor (Seconds), Mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |

Data are mean (SD); N = the number of boys in the analysis set; n = the number of boys meeting the criterion; (%) = n/N*100. Arm span is used in place of height when deriving body mass index for non-ambulant boys/young men
Abbreviations: BMI, body mass index; DCO, data cut off; OLE, open-label extension; SAS, Safety analysis set..
SD, standard deviation.
Source: DoF (Study 51 Clinical Study Report; Dec 2023 DCO).[135]

In section B.2.4.9 of the CS, the company notes that the 'naïve' givinostat group is younger, lighter and had less time since initiation of corticosteroids than givinostat or delayed givinostat groups. The EAG additionally notes that the 'naïve' givinostat group were more likely to use deflazacort and have a daily corticosteroid schedule. The clinical baseline characteristics for the 'naïve' givinostat group [redacted] than the givinostat or delayed givinostat group at OLE baseline. However, compared to the baseline clinical characteristics from Study 43, the OLE 'naïve' group are slightly older and their measures of functional status slightly worse. The EAG note that the 'naïve' givinostat group were eligible for Group B in EPIDYS for which eligibility was based on a VLFF $\leq$ 5% or >30%. However, baseline VLFF is not reported for the 'naïve' givinostat group for OLE, even though it is considered a predictor for loss of ambulation.[31] (Baseline VLFF is not reported for any group in OLE).

#### *3.3.2.3 Interventions*

All participants received givinostat oral suspension 10 mg/mL, twice daily after a meal (dose adjusted according to weight). However, the CS describes OLE as including three 'treatment' groups (givinostat, delayed givinostat and naïve givinostat). For participants already receiving givinostat, 'starting' dose was the same level received at the end of their previous study, under the flexible treatment regimen (See section 3.3.1.3). For OLE participants naïve to givinostat at study entry (including 'delayed' group) treatment was started with 13–47 mg oral givinostat, twice daily. All participants were also continued with ECM.

#### *3.3.2.4 Safety and Efficacy Results*

Safety outcomes were the primary outcome in OLE and included type, incidence, and severity of TRAEs and non-related AEs, and SAEs (EAG Table 5). Results were presented descriptively for the overall OLE cohort, and for each of the three givinostat 'groups'. The CS states that no new safety signals were identified, with most AEs reported to be mild to moderate in intensity, and no life-threatening AEs. A summary of AEs is shown in Table 11.

Secondary endpoints were reported depending on ambulation status. Descriptive results for 6MWT, NSAA total score, 4SC, Time to walk 10 metres (10MWT), TTRFF, mean knee extension and elbow flexion are reported for the overall OLE cohort, and for each of the three givinostat 'groups'. OLE additionally reports time to major disease milestones for participants who were ambulant at study entry for the three 'treatment' groups (Table 12) and the overall population. Analysis on the overall ITT population include age at loss of ambulation (givinostat: 16.7 years, delayed: 17.3 years, naïve: not calculable) and lung function (givinostat: 2 participants required non-invasive respiratory support).

The OLE study protocol[32] pre-specified exploratory analyses to compare efficacy outcomes between the 'delayed' and givinostat groups. No comparison with the 'naïve' group was pre-specified. The CS notes that givinostat effects were comparable between those who received givinostat from enrolment (in EPIDYS or Study 43) and those whose treatment was delayed by 18 months (EPIDYS placebo). Although these are exploratory analyses for OLE,

the EAG considers the comparison between these groups to be informative for givinostat group selection for the uITC and MAIC (section 3.4). These results are mentioned briefly in CS section B.2.6.6 and in more detail in the study's CSR, section 11.3.

The EAG notes a minor discrepancy between the outcomes listed in CS Tables 10 and 14. In CS Table 10, the following OLE outcomes are listed as being included in the model: adverse events of treatment, time to LOA, age at LOA, time to non-invasive ventilation (NIV), age at non-invasive ventilation, time to FVC<1L, age at FVC<1L, time to FVC<30%, and age at FVC<30%. In contrast, CS Table 14 highlights treatment related AEs, age at loss of ambulation, age at non-invasive ventilation, age at FVC<1L, and age at FVC<30%. The EAG consider CS, Table 14 to be more accurate. However, with the exception of TRAEs, the results from OLE only partially inform the economic model, since the 'delayed' group and some of the givinostat group are removed from the cohort before inclusion in the uITC.

**Table 11: Summary of AEs in OLE study (safety analysis set) (Reproduced from CSR, section 12.3.1.1 and CS Table 35)**

| Outcome | Givinostat (n=119) N (events) | Delayed (n=58) N (events) | Naïve (n=30) N (events) |
|---|---|---|---|
| AEs | Not reported by group. overall: n=203 (2,793) | | |
| - leading to withdrawal from study | Not reported by group. overall: n=8 | | |
| - leading to discontinuation of givinostat | Not reported by group. overall: n=9 | | |
| SAEs | Not reported by group. overall: n=52 (64) | | |
| - leading to discontinuation of givinostat | [redacted] | [redacted] | [redacted] |
| - leading to death | Not reported by group. overall: n=2 | | |
| Treatment-related AE | [redacted] | [redacted] | [redacted] |
| - leading to discontinuation of givinostat | [redacted] | [redacted] | [redacted] |
| Treatment-related SAEs | [redacted] | [redacted] | [redacted] |

**Table 12: Ambulation-specific milestones in OLE study (reproduced from CSR section 2, Synopsis)**

| Outcome | Givinostat (n=110) | Delayed givinostat (n=55) | Naïve givinostat (n=30) |
|---|---|---|---|
| Age at loss of 4SC, mean (years) | [redacted] | [redacted] | [redacted] |
| Age at loss of 10MWT>10 sec, mean (years) | [redacted] | [redacted] | [redacted] |
| Age at loss of TTRFF, mean | [redacted] | [redacted] | [redacted] |
| Age at TTRFF>10 sec, mean | [redacted] | [redacted] | [redacted] |

### Table 13: OLE results for the primary and the secondary outcomes that inform the uITC and economic model

| Outcome | Outcome category | Comparison | Analysis population | Result | EAG comments | Company risk of bias | EAG risk of bias |
|---|---|---|---|---|---|---|---|
| **Primary outcome – company highlights as included in economic model** | | | | | | | |
| **Treatment related AEs** | Primary | Overall and for three groups (givinostat, delayed givinostat, naïve givinostat) | Safety analysis set (n=207) | [redacted] | No formal comparison made and results reported descriptively, as per OLE protocol. For the CS, AE data were not used in the uITC but data from the safety analysis set was used in the economic model to inform adverse events in the givinostat arm. | Not assessed. | Not assessed |
| **Other outcomes stated by the company to inform the economic model** | | | | | | | |
| **Age at loss of ambulation** | Secondary | Results for overall and three groups (givinostat, delayed, naïve<br><br>Exploratory analysis comparing givinostat vs delayed groups. | Overall population | In the overall ITT population (N=207; 195 ambulant and 12 non-ambulant at baseline), 78 (37.7%) young men had lost ambulation by the December 2023 DCO; the median age at loss of ambulation was 16.7 years in the givinostat group, 17.3 years in the delayed givinostat group, and not calculable in the naïve givinostat group (CS, Figure 27) | Results are not used directly in the economic model. Data from participants in the 'delayed' group and a subset of the 'givinostat' group (only patients originally enrolled in EPIDYS) plus data from additional EPIDYS participants was used instead. Data from "delayed" givinostat (originally randomised to placebo) and patients originally enrolled in Study 34 was excluded from uITC. | Not assessed | Critical |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | [redacted] | | | |
| **Age at non-invasive ventilation** | Secondary | Results presented for 'givinostat', 'delayed givinostat', 'naïve givinostat' and overall population. Exploratory analysis comparing 'givinostat' and 'delayed' groups. | Overall population | Two participants from the givinostat group reached a need for daytime respiratory support during follow-up (CS, Figure 28). | Data for patients from Study 43 were excluded. The CS notes *"As the lung function outcomes for givinostat are immature, with zero events occurring during the study follow-up period for respiratory support, it is not possible to form a direct comparison with ECM nor to extrapolate the givinostat KM data for these outcomes."* (Section B.2.8.2, p.105). | Not assessed | Insufficient data to assess comparison |
| **Age at FVC<1L** | Secondary | NR | NR | NR | NR | NR | NA |
| **Age at FVC <30%** | Secondary | NR | NR | NR | NR | NR | NA |

#### 3.3.2.4.1 Subgroup analyses

There were no planned subgroup analyses and no post hoc analyses reported in the CS.

### *3.3.2.5 Health-related quality of life*

HRQoL results are reported in CS, B.2.6.6 for the overall OLE population. The company did not collect HRQoL data using EQ-5D, the preferred measure of health-related quality of life in adults in the NICE reference case, but using the PedsQL. The CS reports a slight deterioration of HRQoL (around 5-10%) in both child and parent's scores. Additionally, SF-36 is used for adult subjects, but the company notes data was too limited at this cut-off to draw any conclusions. The EAG notes the PedsQL results do not inform the economic model. In clarification question B10, the EAG sought to explore scenarios incorporating trial-based utilities, achieved by mapping of Peds-QL to EQ-5D. See section 4.2.7 of the EAG report.

### *3.3.2.6 Protocol deviations*

Protocol deviations are not reported in the CS, but they are presented in section 10.2 of the OLE CSR. For the overall population (n=207), 231 major protocol deviations were reported (one patient could have more than one major protocol deviation). The most common deviation category was "procedural" (n=102), which included deviations related to study procedures (e.g. assessments not performed or visits not done). Missing data for reasons other than being non-ambulatory or physically unable to perform the test/assessments were imputed using the mean (or mode) of all non-missing values for the respective measurement and time-point across all relevant subjects in the treatment group. Missing data due to being non-ambulatory or otherwise physically unable to perform the test or assessment were imputed by setting the value to zero or to twice the maximum non-missing value across all subjects depending on the directionality of the test. The impact of these deviations is considered in the OLE risk of bias assessment (Section 3.3.2.7).

### *3.3.2.7 Risk of Bias assessment (ROBINS-I)*

In the CS Appendix (D.2.2.1), the company assesses risk of bias for OLE at the study-level, based on the NICE process and methods guidance [PMG24] Section 2.5.[33] The company's assessment did not highlight any concerns with the OLE study and it is reproduced in EAG report appendix alongside the EAG's assessment, using the same criteria. However, the assessment was conducted at the study-level and not the outcome-level and the EAG do not consider the assessment to have used an "appropriate and validated quality assessment instrument".[33] OLE is a non-randomised, uncontrolled study. However, although the primary clinical objective of OLE is not comparative, comparisons between the givinostat and 'delayed' givinostat groups are nevertheless pre-specified as exploratory secondary analyses. A hazard ratio is reported for age at LOA for the givinostat versus the delayed givinostat group HR [redacted] (CSR, Table 41). For the purpose of the CS, an informal comparison is also made between all three 'treatment' groups in OLE for age at LOA (CS, Figure 27). The Kaplan-Meier curves for each 'treatment' group (givinostat, delayed and naïve) are reproduced in EAG Figure 3. As OLE is a non-randomised study, the EAG used the ROBINS-I tool to assess risk of bias in the LOA outcome, as informed by the

KM curves and HR estimate. The EAG assessment is reported in Appendix 1.1 and summarised here.

Overall risk of bias was judged to be critical for age at LOA in the OLE study. Risk of bias due to confounding was judged to be serious, as OLE is not a randomised study, and there are differences in prognostic factors and baseline characteristics between the 'treatment' groups that are not controlled for in the results reported in the CS. Risk of bias due to selection of participants into the study was judged to be critical, due to the likelihood that there were post-intervention variables that influenced selection. For example, a higher proportion of patients who had not previously received givinostat were enrolled into OLE. The EAG note concerns regarding the start of follow-up and intervention not coinciding for participants from EPIDYS and Study 43. Bias in selection of the reported results in the CS was judged to be serious. Participants were assigned to their respective interventions, and received them for the duration of their primary studies before starting follow-up in OLE. Selection into the OLE givinostat group is also dependent on having completed EPIDYS and Study 43, which is a characteristic observed after starting intervention and reasons for not enrolling are not provided in the CS (23 participants from earlier studies did not enrol in OLE, see Figure 2). Bias in classification of interventions, deviation from intended interventions and in measurement of outcomes was judged to be low.

## 3.4 Critique of evidence and methods used for unanchored indirect comparisons

As described in section 4.2 of the EAG report, the company's preferred economic model structure is that of the Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis) natural history model. In terms of the clinical effectiveness evidence reported in the CS, the EAG note that a key issue with the HERCULES model structure is that neither the primary outcome of EPIDYS (4SC) nor any of the other outcomes collected during the randomised phase of the trial can be utilised to directly inform the transition rates between the health states in the model. The EAG's full critique of the economic model is reported in section 4.2 of this report. The outcomes of interest for the uITC were age at LOA, age at NIV and age at FVC<1L.

The company SLR did not find any additional RCT evidence and the company therefore use a uITC and MAIC to estimate the efficacy for longer-term outcomes on givinostat relative to ECM. Whilst the EAG agrees that there is an absence of comparative data for long-term outcomes, there is randomised evidence from EPIDYS and NICE TSD 18 notes that randomised evidence is preferred where available.[34] The EAG preferred approach would be to apply relative treatment effects estimated from EPIDYS to a suitable natural history baseline, rather than disregarding the comparative data available from the randomised EPIDYS trial (as is done when using the uITC). Further discussion is in section 3.5.3.

### 3.4.1 Studies included / excluded from the unanchored indirect comparisons

Studies included in the uITC were identified and appraised as part of the clinical effectiveness SLR. As described in section 3.1, the EAG consider that the searches were appropriate to identify RCTs and observational studies (e.g. registry or cohort studies to estimate natural history) and that the conduct of the review was adequate. In terms of identifying RCTs (and linked clinical studies) the company SLR identified one published journal article (and several posters/abstracts) relating to the company's own Phase 3, randomised placebo-controlled study (EPIDYS, Study 48)[19] and to the company's open-label extension study to EPIDYS (OLE, Study 51).[20] EPIDYS and OLE were used to inform estimates for givinostat. However, the EAG have concerns about the transparency of the study selection process with regards identification of 'real-world' registry or cohort studies to inform the ECM estimate in the uITC and MAIC. Appendix D.2.3 of the CS, lists 37 potential studies were identified in the SLR on the natural history of DMD from which two are discussed in the CS: a UK registry study[18] and the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS).[35] However, no details are provided for the exclusion of the other 35 references. The EAG raised a clarification query about one paper (Zambon et al, 2022)[36] in clarification question A18.

The CS describes the UK registry data as a "published UK real-world data source" (CS, Document B. p.98) and notes that a UK source is most appropriate to estimate efficacy of ECM in UK patients. For estimating comparative treatment efficacy, the EAG consider that it is most appropriate to use a source of evidence that more closely balances prognostic factors with EPIDYS/OLE and effect modifiers with the target population. For estimating a natural history baseline, it is most appropriate to use a source of evidence that most closely resembles the effect of ECM in the target population. Holding all factors constant, e.g data collection methods, sampling, sample size, available characteristics, the EAG agree that a UK source of routine data would be preferable for the natural history baseline. However, the study cited is based on a retrospective case note review and the publication noted in the CS is a conference abstract with limited details on the characteristics of registry participants.[18] Pietrusz et al[18] included 209 patients from three UK hospitals (in London, Newcastle and Oxford) to evaluate the effect of continuing corticosteroid treatment on pulmonary function. Data was collected between February 2020 and July 2022. A slide deck of the conference presentation was available to the EAG as part of the company submission.

As detailed in CS Appendix D, CINRG DNHS is a prospective, longitudinal study with patients aged 2–28 years with confirmed DMD, across 20 centres in nine countries. 340 participants were recruited between May 2005 and July 2009. An additional 100 participants, between 4 and 8 years old, were enrolled between 2012 and 2016.[37] The CINRG DNHS is described by study investigators as the largest prospective multicentre natural history study of DMD. However, it does not appear that any of the recruiting centres were located in the UK.

### 3.4.2 Critique of data sources identified and included in unanchored indirect comparison

#### *3.4.2.1 Sources to inform estimates for givinostat*

The company studies identified in the CS SLR and critiqued by the EAG in Section 3.3 inform the givinostat 'arm' of the uITC and MAIC. Figure 2 provides a visualisation of how the company's studies feed into the uITC. To form a givinostat group for the uITC, the company combine data from the givinostat arm of EPIDYS (n= 118) and the 'naïve' givinostat group from OLE (n=30). The EAG has several, related concerns, about the selection of participants to form the givinostat group for the uITC. The CS states that patients in the two studies were eligible to be included in the uITC if they had received givinostat from study entry. This means that those in the 'delayed' group in OLE were excluded from the uITC (those who had received placebo in EPIDYS). The CS states this is because treatment effect in those patients will be confounded (due to the impact of having taken placebo prior to starting givinostat). However, as seen in Figure 3, (reproduced from CS, Figure 27) and from the exploratory analysis for age at LOA (EAG, Table 13) the delayed givinostat group appear to perform similarly to the continuous givinostat group ([redacted]. Whilst the numbers of participants and events likely mean the comparison is statistically underpowered, this exploratory analysis suggests that the groups may be comparable.

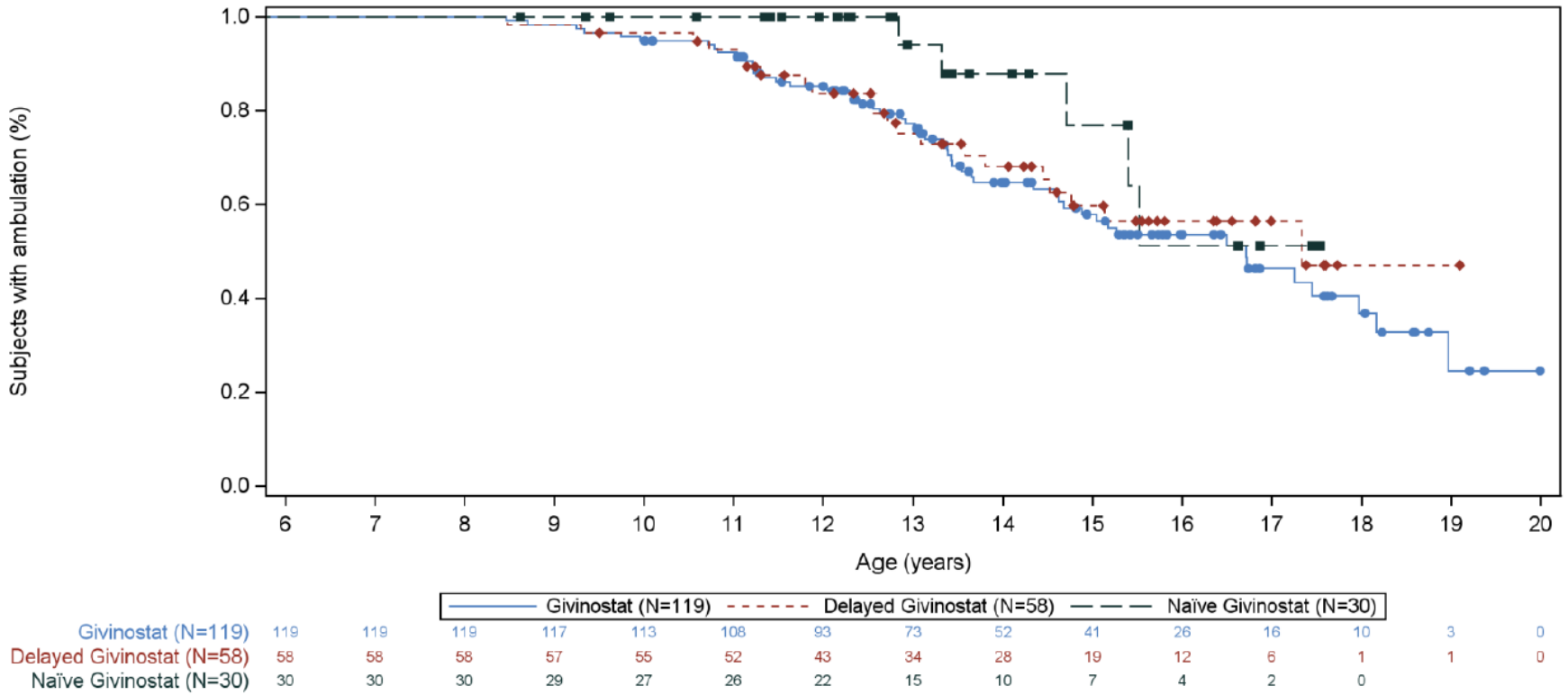
Although the 'naïve' givinostat group were eligible to be randomised in EPIDYS, they were not and, as noted in 3.3.2.2, baseline characteristics for the 'naïve' group at OLE study entry were indicative of an earlier disease stage and less time since initiation of corticosteroids. This group may therefore have a better prognosis than those in EPIDYS, and may impact the generalisability of OLE to a UK population. Furthermore, if the impact of receiving placebo prior to givinostat (the 'delayed' givinostat group) causes confounding (as reported by the company), then it is likely that delaying entry to the study for many months may also have a confounding effect. The CS does not report results for a comparison between the naïve and delayed, or naïve and givinostat groups. However, as seen in Figure 3 (reproduced from the CS, Figure 27), the naïve givinostat group appear to have a more favourable profile in terms of age at LOA. The EAG consider that combining the naïve and givinostat patients into a single 'givinostat' group in the uITC, but excluding the delayed givinostat patients, is not robustly justifiable. It likely slightly favours givinostat by increasing the age at LOA. However, the EAG acknowledges that sample sizes are too small to confirm this statistically.

Although participants in Study 43 met the criteria of having received givinostat from study entry, the CS excludes them from the uITC. However, as the CS notes, a primary motivation for the uITC and MAIC is *"the absence of comparative data for long-term outcomes*" (CS Document B, p.98). The EAG notes that the exclusion of Study 43 seems contradictory to that stated aim. Study 43 participants have the longest follow-up and the longest time on treatment, and so may provide important information. On balance, the EAG consider that excluding Study 43 participants, is likely to be reasonable given the different inclusion criteria, baseline characteristics indicating less progressed disease, and treatment dosing regimen. However, the EAG also note that the combined median age at LOA for the 'givinostat' group in OLE (i.e. the combined EPIDYS and Study 43 group) was 16.7 years

(95%CI: 14.6 to 18.2) compared to 18.0 years (95%CI: 15.4 to Not estimable) (CS, sections B.2.6.6 and B.2.8.4) for the uITC givinostat group. As such, a sensitivity analysis to explore the impact of having included all OLE participants in the givinostat group is recommended, irrespective of their study of origin.

### Key Issue 3 Post-hoc selection of givinostat patients

**Figure 3: Kaplan-Meier plot of age at loss of ambulation | ITT set. Reproduced from company submission Figure 27.**




Abbreviations: ITT, intention-to-treat

#### *3.4.2.2 Sources to inform estimates for established clinical management*

To form an ECM group for the uITC, the company used data obtained from a retrospective case review of a UK registry study.[18] The CS also considers data from the CINRG DHNS and a sensitivity analysis was reported in CS, Appendix D.2.8.1. The company chose not to use this study for the base-case because it was not as recent as the UK registry study and it was not conducted in UK centres.

The UK registry included 156 patients of whom 53 were corticosteroid naïve (use ≤12 months); 43 had stopped corticosteroid (>12 months but stopped prior to transition to adult services); and 113 continued corticosteroid use into adulthood. The CS notes that there was minimal availability of baseline characteristics in the UK registry data and only age at start of corticosteroid use was reported. No further information about ECM or concomitant treatments was reported. No explicit definition of non-ambulatory patients for the registry is reported in the CS. However, the EAG note that the Pietrusz presentation[58] provided as Data on File with the CS, implies that wheelchair use was an important characteristic. (It states: [redacted]", Slide 3).

In clarification question A18, the EAG drew attention to the DMD UK North Star Network registry, as it includes data on additional functional covariates that the company say were not available for use in the MAIC. The North Star Network is a network of 23 UK neuromuscular centres, and the longitudinal registry was established in 2006 with prospective data collection. In clarification question A18, the EAG noted that registry data had been used in a 2022 paper examining peak functional ability and age at loss of ambulation in DMD[36] and that longitudinal data on additional functional variables, NSAA total score, TTRFF and VL MFF were available. In response, the company noted that the non-ambulatory measures were not available in Zambon et al (i.e. age at NIV and age at FVC<1L). The EAG accepts the company response that data were not available in the Zambon paper. However, non-ambulatory data of interest are available via the North Star registry.[38]

The CINRG DHNS registry data considered in the CS was based on 261 participants from CINRG who had been matched to participants in the STRIDE ataluren registry in a previous analysis. In that analysis, CINRG DHNS participants who had previously been enrolled in ataluren trials were excluded. Participants in the matched sample were aged 5 years and older and were receiving concomitant medication. The unmatched CINRG DHNS population n= 398 had mean age at first symptoms in CINRG DHNS was 3.23 (SD 1.68) and mean age of first corticosteroid used was 6.73 (SD 2.05). The unmatched number of participants using deflazacort ≥12 months was n=145 and other corticosteroids n=160. Non-ambulatory patients were defined as those who required full-time use of a wheelchair.[39]

In the EAG's view, if the aim is to reliably approximate an ECM 'arm', then the key limitation of *both* the UK registry and CINRG DHNS data sources is the limited number of baseline characteristic summaries available to match the EPIDYS/OLE data to, or to confirm similarity between the populations. In the UK registry study, summary statistics were only reported

for one variable, corticosteroid starting age. This was quite different from the EPIDYS/OLE data. For the CINRG DHNS, summary statistics for additional variables were reported: age at diagnosis (years), corticosteroid start age, duration of deflazacort use, duration of other corticosteroid use. A large number of other baseline characteristics available in EPIDYS/OLE were not reported in either the UK registry study or CINRG DHNS, many of which are likely to be important prognostic factors (CS, Table 24).

Although Kaplan-Meier curves were available for age at NIV and age at FVC<1L in the UK registry study, no curve was available for age at LOA. Acceleration factors therefore were used to extrapolate Kaplan-Meier data for age at LOA, both for use in the natural history baseline and the uITC, which required several key assumptions (Section 3.4.3.1). CINRG DHNS provided Kaplan-Meier data on both age at LOA and pulmonary outcomes (age at pFVC <50%, pFVC <30% and FVC <1L), which therefore did not require use of acceleration factors for extrapolation. However, age at NIV was not provided in this study. The company used age at pFVC <50% as a proxy for this in their sensitivity analyses.

The EAG acknowledge the relevance of a UK data source, particularly to inform the natural history baseline. However, for estimating comparative treatment efficacy, and given the importance of ensuring that all important prognostic factors are accounted for in a uITC, the EAG note that there may be greater similarities between EPIDYS/OLE and CINRG DNHS than between EPIDYS/OLE and the UK registry study. The EAG therefore prefer to use the EPIDYS/OLE givinostat data, matched to CINRG DNHS as an external control to estimate comparative effectiveness. Primary reasons for the EAG's preference of using EPIDYS/OLE matched to CINRG DHNS to estimate comparative treatment efficacy are:

- **Potential difference in efficacy between prednisolone and deflazacort (in ECM patients):** Prednisolone is more commonly used in UK, whereas deflazacort more commonly used in EPIDYS/OLE (81%). Whilst the proportion of patients on deflazacort was not reported in the UK registry study, it would be expected to be much lower than in EPIDYS/OLE. In CINRG DHNS the proportion of patients on deflazacort (51%) is lower than in EPIDYS/OLE, but it is likely higher than the UK registry, and since the value is reported it is possible to match on this characteristic (though the EAG acknowledge that covariate overlap is poor for matching). The EAG note there is conflicting evidence in the wider literature regarding whether the effect of prednisolone/prednisone and deflazacort differ.[24, 25]
- **Additional prognostic factors available for matching:** CINRG DHNS has additional prognostic variables to match on compared to the UK registry, relating to corticosteroid use and age at diagnosis. These appear to have a substantial impact (Section 3.4.4.1.2), suggesting (in addition to clinical expertise) that they are important prognostic factors.
- **Global nature of CINRG DHNS matches better with multi-centre EPIDYS/OLE:** The global nature of CINRG DHNS, whilst making it less suitable for estimating natural history baseline, aligns more with the multi-centre international nature of EPIDYS,

which only included 8 (6.7%) patients in the UK. This is likely to mean that other unobserved prognostic factors relating to this are more likely to be balanced between the populations.

**Key Issue 4: What is the most appropriate source of data to inform comparative treatment efficacy?**

### 3.4.3 Methods used for unanchored indirect comparisons

The company performed several MAIC to reweight the givinostat patients to the average prognostic factors in the UK registry data study using propensity score matching.

The company attempted to match on key prognostic factors that were available from the registry data sources. Due to the limited availability of information on prognostic factors only age at corticosteroid use was available for matching in the UK registry study, meaning that other important prognostic factors and effect modifiers (age at diagnosis; genotype; baseline functional, cardiac and respiratory status), are likely to have differed between the givinostat and ECM populations, which may have explained the differences observed in age at LOA. Furthermore, trials typically include healthier patients than the target patient population, leading to more favourable prognosis in trial participants. Matching a trial population to a registry study is therefore likely to further lead to imbalance in unobserved prognostic factors due to differences in inclusion/exclusion criteria.

For the CINRG DNHS registry there were two additional variables reported, which were age at diagnosis (years) and the proportion of patients with deflazacort use $\geq$ 12 months. In sensitivity analyses, matching to the CINRG DNHS using these additional variables was shown to reverse the direction of effect of weighting on givinostat, making results less favourable than in the company's base-case (see Section 3.4.4).

Within the MAIC, several of the rescaled weights were >2, indicating that these participants will have been assigned a disproportionately large weight in the analyses (CS, Appendix Figure 7). Whilst important to note, the EAG did not expect this to have a substantial impact on results given that the number of weights >2 was small in number.

When presenting weighted hazard ratios (HR)s for givinostat versus ECM, the company used both bootstrap and robust sandwich estimators to account for the fact that the weights are estimated. The company highlighted results in bold to indicate a significant difference between treatments, although the EAG note that, because the propensity score model informing MAIC weights only includes covariate means, the populations are not matched on covariate variances. This is likely to lead to some bias in an unknown direction in the 95% CIs of the HRs (and of the median time-to-event results), such that concluding statistical significance in this way is not valid.

#### *3.4.3.1 Extrapolation of outcomes using acceleration factors*

Whilst age at LOA was available from EPIDYS/OLE, the follow-up was not long enough to provide data on age at NIV and age at FVC <1L. The EAG note that analysis of age at NIV and age at FVC <1L (and therefore the extrapolation of givinostat outcomes) for use in the economic model *is only necessary if a direct treatment effect of givinostat is directly assumed to occur in non-ambulatory states*.

To generate the relevant Kaplan-Meier curves on outcomes for which they were not reported, the company applied acceleration factors to different outcomes, within the different datasets. These were derived by dividing the reported median time-to-event for one outcome (e.g. age at LOA) by the medians of another outcome (e.g. age at NIV) within the UK registry data, and were then applied to the Kaplan-Meier data of age at LOA to estimate the Kaplan-Meier data for the other outcomes in the givinostat patients (Table 14). Kaplan-Meier data was also not available for age at LOA in the UK registry study, and so an acceleration factor was used to estimate this from the age at NIV Kaplan-Meier data.

Use of acceleration factors in this way assumes that the shapes of the survival curves are the same, and also that the acceleration factors are the same between givinostat and ECM, and between the EPIDYS/OLE and UK registry study populations (prior to matching). It further makes the assumption that if givinostat has an effect on age at LOA, it will also have an effect on age at NIV and age at FVC <1L. Given that data for givinostat on age at NIV and age at FVC <1L are immature, there is no evidence to support this assumption. Whilst the company provides references to demonstrate that age at LOA has been shown to be predictive of absolute FVC,[35, 40, 41] this is highly uncertain, and it is unclear what benefits a treatment effect on age at LOA might provide for subsequent non-ambulatory outcomes (age at NIV and age at FVC <1L).

Following a request from the EAG during clarification (clarification question A15), the company provided sensitivity analyses using acceleration factors derived from the CINRG DNHS (Table 14). Whilst these supported the proportional time-to-event relationships between the outcomes in the ECM population, they did not differ substantially from acceleration factors derived from the UK registry study (and thus did not fully explore the sensitivity of the acceleration factor values). They also still made the strong assumption that the relationships between outcomes in givinostat were the same as those observed in ECM. Results for these sensitivity analyses are given in Section 3.4.4.4.2.

**Table 14: Derivation and use of acceleration factors to estimate Kaplan-Meier curves for different outcomes. Reproduced with modifications* from CS, Table 26**

| Outcome | Givinostat data | ECM data | AFT estimate (company base-case) | AFT estimate (CINRG DNHS – company sensitivity analysis) |
|---|---|---|---|---|
| Age at LOA | Age at LOA KM | Age at NIV KM with AF applied | CS stopped = 0.67<br>CS continued = 0.66 | 0.73 |
| Age at NIV | Age at LOA KM with AF applied | Age at NIV KM | 1.50† | 1.37 |
| Age at FVC <1L | Age at LOA KM with AF | Age at FVC <1L KM | 1.94† | 1.91 |

*Modification: company sensitivity analyses added to table
†Estimates for ECM from combined CS stopped and continued groups.
Abbreviations: 1L, one litre; AFT, acceleration factor; CS, corticosteroids; ECM, established clinical management; FVC, forced vital capacity; KM, Kaplan-Meier; LOA, loss of ambulation; NIV, non-invasive ventilation.

### 3.4.4 Results of the unanchored indirect comparisons

Table 15 presents the givinostat studies (unadjusted and weighted) and baseline characteristics for ECM for the conducted analyses in the company's base case (matching to the UK registry study) and the EAG's base case (matching to CINRG DNHS). Whilst the reduction in ESS due to matching to the UK registry study was moderate, there was substantial reduction in ESS when matching to the CINRG DNHS, due to matching on two additional baseline characteristics for which there was poor overlap. Although the EAG believe that adjusting for these two additional prognostic factors is essential, the degree of overlap raises concerns for use of the CINRG DNHS dataset, as it means that a small number of individuals in EPIDYS/OLE will be given a substantially large weighting in the analysis.

**Table 15: Comparison of baseline characteristics: givinostat (EPIDYS and OLE Study) vs. ECM, weighted to both the UK registry study and CINRG DNHS**

| Target population | Treatment arm | N/ESS | CS start age (years); mean | Age at diagnosis; mean | Deflazacort use duration ≥12 months; % |
|---|---|---|---|---|---|
| | Givinostat unadjusted | 148.0 | 6.09 | 4.17 | 81% |
| UK registry study | Givinostat weighted | 105.1 | 7.20 | - | - |
| | ECM | 156.0 | 7.20 | - | - |
| CINRG DNHS | Givinostat weighted | 37.2 | 6.50 | 2.89 | 46% |
| | ECM | 261 | 6.50 | 2.89 | 46% |

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; CS, corticosteroids; DNHS, Duchenne Natural History Study; ECM, established clinical management; ESS, effective sample size;

#### *3.4.4.1 Age at loss of ambulation*

##### 3.4.4.1.1 Company base case

Table 16 shows the HRs and median age at LOA, and Figure 4 shows the Kaplan-Meier plot for age at LOA for both unweighted and weighted givinostat patients, versus ECM, in the company base case. These indicated a substantially later age at LOA for patients receiving givinostat than for those on ECM. In the company's base-case (ECM informed by the UK registry study) the impact of weighting using the unanchored MAIC was to slightly further increase the age at LOA (improving the favourability of givinostat), though this impact differed between the company and the EAG's base case. Data for givinostat were relatively immature, and median age at LOA was not reached in the weighted givinostat patients.

**Table 16: Summary of age at LOA MAIC (company base case): givinostat (EPIDYS/OLE) vs. ECM (UK registry study). Reproduced from CS, Table 28.**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 17.97 (15.40, NE) | 0. 222 (0.153, 0.323) |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NE (15.52, NE) | Robust SE: 0.185 (0.121, 0.282) Bootstrap: 0.184 (0.127, 0.261) |
| ECM (UK real-world data) | 156.0 | 79 | 12.28 (11.74, 13.13) | Comparator |

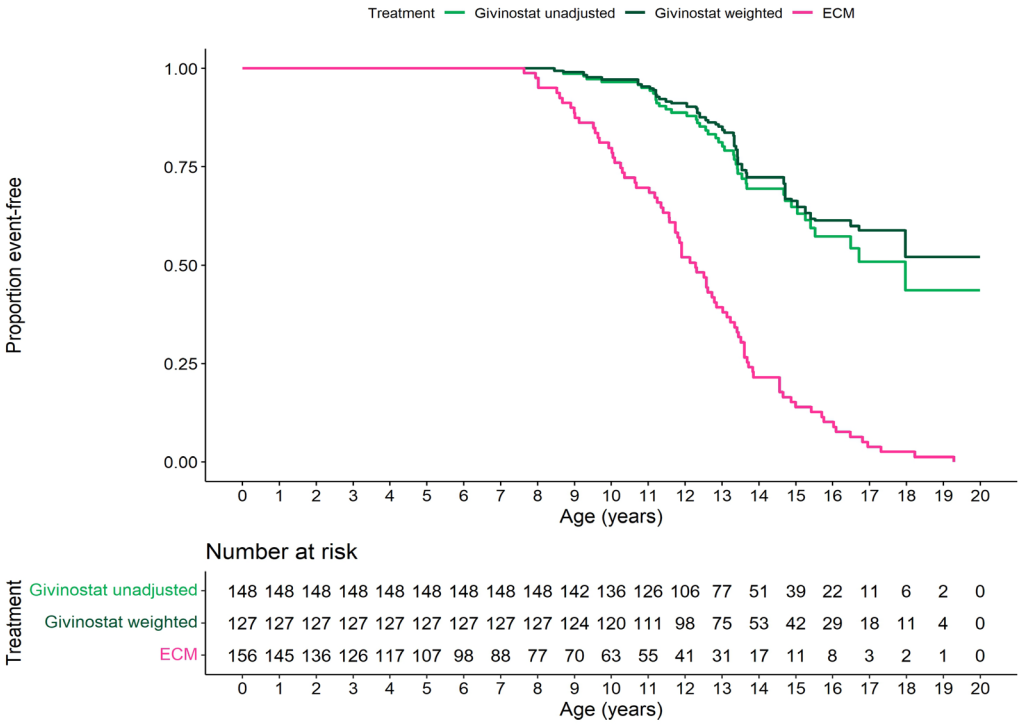
CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.

##### 3.4.4.1.2 EAG base case

In the EAG base case (company sensitivity analysis), the effect of weighting was substantially greater and the direction was reversed in the sensitivity analysis comparing givinostat to ECM informed by CINRG DNHS (Section 3.4.4.4). The EAG base case matched givinostat patients from EPIDYS/OLE to ECM patients from CINRG DHNS, instead of to ECM patients from the UK registry study. Weighted and unweighted HRs and the median age at LOA (Table 17) are shown for givinostat versus ECM for both the MAIC weighted to CINRG DHNS (EAG base-case) and the MAIC weighted to the UK registry study (company base-case). Kaplan-Meier plots for the givinostat data weighted to CINRG DHNS are shown in CS Appendix (Figures 3 and 6)

The unadjusted HR for givinostat versus ECM is slightly higher for the comparison to the CINRG DHNS than to the UK registry study, due to the slightly improved survival in this data source. However, the effect of the weighting is markedly different between the two analyses, with matching to the CINRG DHNS resulting in a substantially increased HR for givinostat versus ECM and reduced median age at LOA on givinostat (Table 17).

**Figure 4: Kaplan-Meier plot for age at LOA MAIC: givinostat (EPIDYS/OLE) vs. ECM (UK registry study). ECM age at LOA derived from age at NIV using an acceleration factor. Reproduced from CS, Figure 31.**




Abbreviations: ECM, established clinical management; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; OLE, open-label extension; UK, United Kingdom

**Table 17: Summary of age at LOA MAIC sensitivity analysis: givinostat (EPIDYS/OLE) vs. ECM (CINRG DHNS or UK registry study)**

| Treatment | Matched to CINRG DHNS (EAG base case) | | Matched to UK registry study (company base case) | |
|---|---|---|---|---|
| | Median (95% CI) | Givinostat vs. ECM HR (95% CI) | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
| Givinostat unadjusted (EPIDYS / OLE study) | 17.97 (15.40, NE) | 0.346 (0.245, 0.488) | 17.97 (15.40, NE) | 0.222 (0.153, 0.323) |
| Givinostat weighted (EPIDYS / OLE study) | 16.49 (13.67, NE) | Robust SE: 0.469 (0.257, 0.855)<br>Bootstrap: 0.451 (0.249, 0.832) | NE (15.52, NE) | Robust SE: 0.185 (0.121, 0.282)<br>Bootstrap: 0.184 (0.127, 0.261) |
| ECM | 13.01 (12.01, 14.00) | Comparator | 12.28 (11.74, 13.13) | Comparator |

Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.

#### *3.4.4.2 Age at non-invasive ventilation*

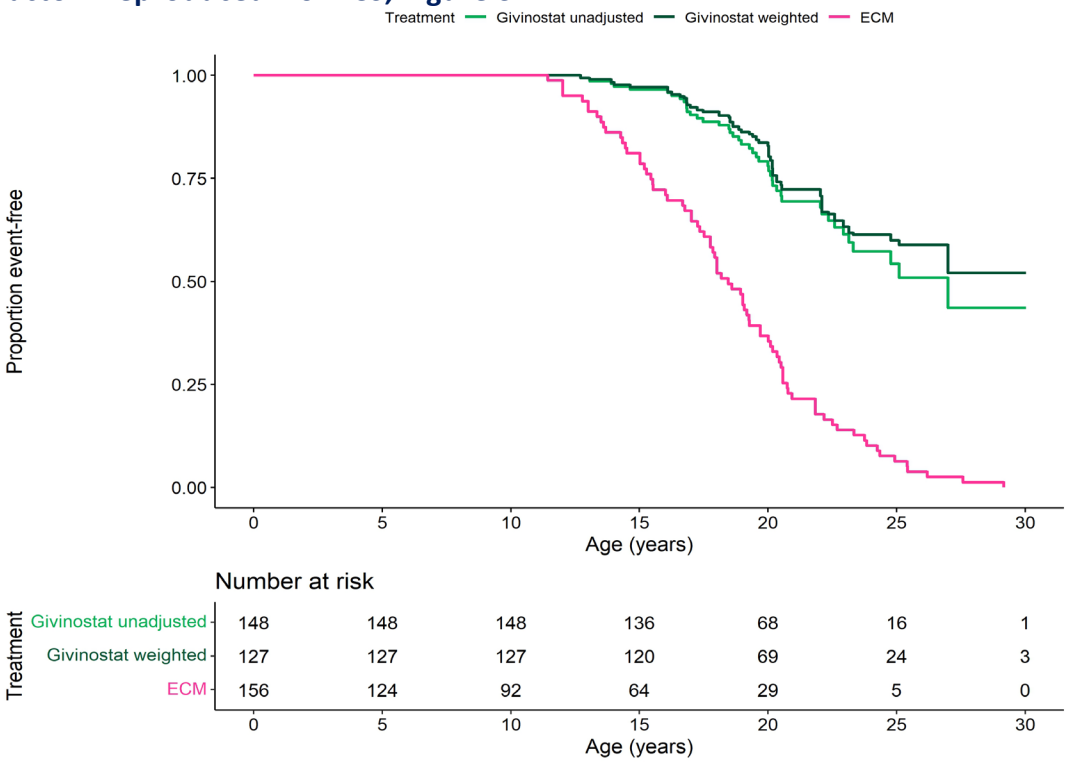
Table 18 shows the HRs and median age at NIV, and Figure 5 shows the Kaplan-Meier plot for age at NIV for both unweighted and weighted givinostat patients, versus ECM. These indicated a substantially later age at NIV for patients receiving givinostat than for those on ECM. In the company's base-case (ECM informed by the UK registry study) the impact of weighting using the unanchored MAIC was to slightly further increase the age at NIV (improving the favourability of givinostat), though the effect of weighting was substantially greater and the direction was reversed in the sensitivity analysis comparing givinostat to ECM informed by CINRG DNHS (Section 3.4.4.4). Data for givinostat were relatively immature, and median age at NIV was not reached in the weighted givinostat patients.

**Table 18: Summary of age at NIV MAIC: givinostat (EPIDYS/OLE) vs. ECM (UK registry study). Reproduced from CS, Table 29**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 27.00 (27.14 to NA) | 0.228 (0.157, 0.332) |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NA (23.32 to NA) | Robust SE: 0.190 (0.124, 0.290) Bootstrap: 0.191 (0.130, 0.264) |
| ECM (UK real-world data) | 156.0 | 79 | 18.46 (17.76 to 19.70) | Comparator |

Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; NE, not evaluable; OLE, open-label extension; SE, standard error.

**Figure 5: Kaplan-Meier plot for age at NIV MAIC: givinostat (EPIDYS/OLE) vs. ECM (UK registry study). Givinostat age at NIV derived from age at LOA using an acceleration factor. Reproduced from CS, Figure 32**



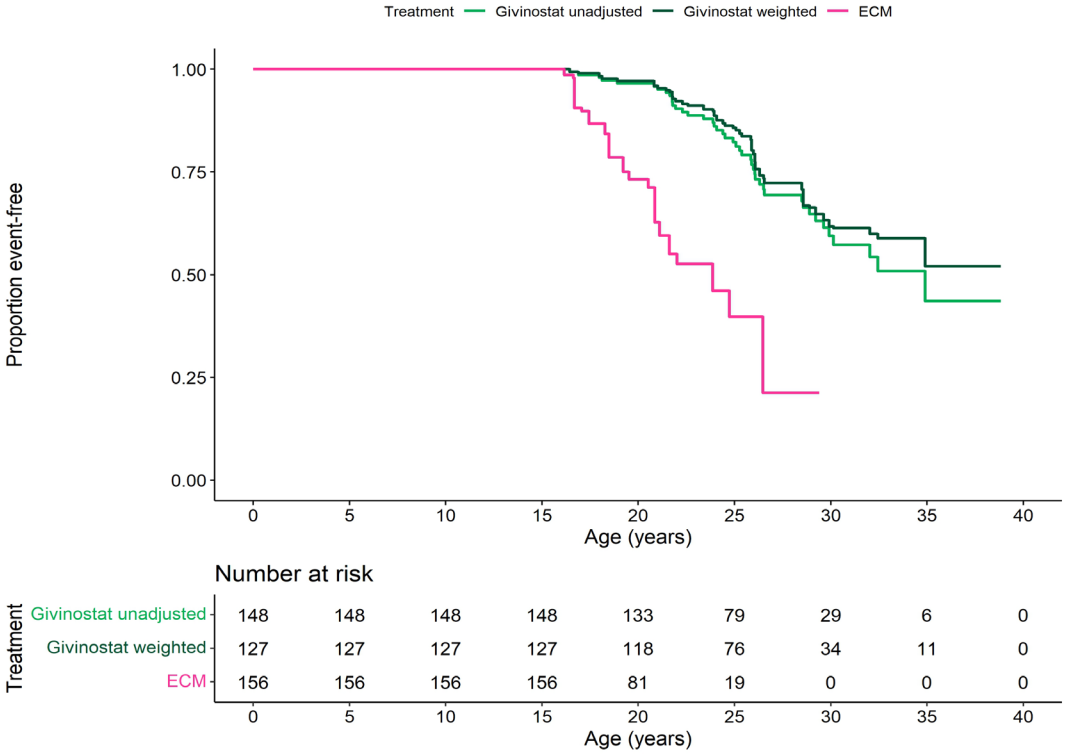

Abbreviations: ECM, established clinical management; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; OLE, open-label extension; UK, United Kingdom.

**Table 19: Summary of age at FVC <1L MAIC: givinostat (EPIDYS/OLE) vs. ECM (UK registry study). Reproduced from CS, Table 29.**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (EPIDYS/OLE study) | 148.0 | 43 | 34.90 (29.91, NA) | 0.233 (0.154, 0.353) |
| Givinostat weighted (EPIDYS/OLE study) | 105.1 | 36 | NA (30.14, NA) | Robust SE: 0.214 (0.139, 0.329) Bootstrap: 0.214 (0.151, 0.288) |
| ECM (UK real-world data) | 156.0 | 67 | 23.86 (21.62, 26.47) | Comparator |

Abbreviations: 1L, 1 litre; CI, confidence interval; ECM, established clinical management; ESS, effective sample size; FVC, forced vital capacity; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; NE, not evaluable; OLE, open-label extension; SE, standard error.

**Figure 6: Kaplan-Meier plot for age at FVC<1L MAIC: givinostat (EPIDYS/OLE) vs. ECM (UK registry study). Givinostat age at FVC<1L derived from age at LOA using an acceleration factor. Reproduced from CS, Figure 33.**




Abbreviations: 1L, 1 litre; ECM, established clinical management; FVC, forced vital capacity; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; OLE, open-label extension; UK, United Kingdom.

#### *3.4.4.3 Age at FVC <1L*

Table shows the HRs and median age at FVC<1L, and Figure 6 shows the Kaplan-Meier plot for age at FVC<1L for both unweighted and weighted givinostat patients, versus ECM. These indicated a substantially later age at FVC<1L for patients receiving givinostat than for those on ECM. In the company's base-case (ECM informed by the UK registry study) the impact of weighting using the unanchored MAIC was to slightly further increase the age at FVC<1L (improving the favourability of givinostat), though the effect of weighting was substantially greater and the direction was reversed in the sensitivity analysis comparing givinostat to ECM informed by CINRG DNHS (Section 3.4.4.4). Data for givinostat were relatively immature, and median age at NIV was not reached in the weighted givinostat patients.

#### *3.4.4.4 Company sensitivity analyses*

##### 3.4.4.4.1 Matching to CINRG DHNS

The company performed sensitivity analyses in which they matched givinostat patients from EPIDYS/OLE to ECM patients from CINRG DHNS, instead of to ECM patients from the UK registry study. As explained in Section 6.3, for age at LOA this was the EAG's base case. However, given that a treatment effect was not assumed for age at NIV and age at FVC<1L in the EAG's base case, we refer to MAIC analyses of these outcomes matched to CINRG DHNS as company sensitivity analyses. Weighted and unweighted HRs and the median age

at FVC<1L (Table 20) are shown for givinostat versus ECM for both the MAIC weighted to CINRG DHNS (company sensitivity analysis) and the MAIC weighted to the UK registry study (company base-case). A Kaplan-Meier plot for the givinostat data weighted to CINRG DHNS is shown in CS Appendix, Figure 6.

For age at FVC<1L, the unadjusted HRs for givinostat versus ECM are very similar in both analyses, yet the effect of the weighting is (similarly to age at LOA) markedly different between the two analyses, with matching to the CINRG DHNS resulting in a substantially increased HR for givinostat versus ECM and reduced median age at FVC<1L on givinostat (Table 20). sThe EAG also notes that the median age at FVC<1L are different for both the sensitivity analyses and company base-case for the unadjusted givinostat patients. This group of patients should be identical in both analyses, so the medians should be identical. The EAG was initially unclear why these values are different, since it suggests that a slightly different subset of givinostat patients may have been included in each analysis. The company provided a clarification during the Factual Accuracy Check, that the median ages were different because of the study-specific AFT multiplier applied to age at LOA, which varies across these analyses.

This sensitivity analysis demonstrates that use of a different source of data for ECM and adjusting for additional baseline characteristics (age at diagnosis, proportion of deflazacort use ≥12 months) completely reverses the directional effect of the weighting, leading to a substantial worsening of the givinostat versus ECM treatment effect. The low ESS in the MAIC using CINRG DHNS (resulting from matching on additional baseline characteristics) further highlights the substantial uncertainty in performing an uITC for this appraisal.

**Table 20: Summary of age at FVC<1L MAIC sensitivity analysis: givinostat (EPIDYS/OLE) vs. ECM (CINRG DHNS or UK registry study)**

| Treatment | Matched to CINRG DHNS (company sensitivity analysis) | | Matched to UK registry study (company base case) | |
|---|---|---|---|---|
| | Median (95% CI) | Givinostat vs. ECM HR (95% CI) | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
| Givinostat unadjusted (EPIDYS / OLE study) | 34.37 (29.46, NE) | 0.251 (0.154, 0.409) | 34.90 (29.91, NA) | 0.233 (0.154, 0.353) |
| Givinostat weighted (EPIDYS / OLE study) | 31.54 (26.15, NE) | Robust SE: 0.406 (0.196, 0.843)<br>Bootstrap: 0.397 (0.213, 0.730) | NA (30.14, NA) | Robust SE: 0.214 (0.139, 0.329)<br>Bootstrap: 0.214 (0.151, 0.288) |
| ECM | 24.88 (21.88, NE) | Comparator | 23.86 (21.62, 26.47) | Comparator |

Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.

#### 3.4.4.4.2 Use of different acceleration factors

Table 21 shows the results of the sensitivity analysis using different acceleration factors, derived from CINRG DHNS (clarification question A15). Although differences in the derived acceleration factors between the two data sources were modest, those from CINRG DHNS were typically closer to 1 than those from the UK registry study, suggesting smaller proportional time-to-event differences in CINRG DHNS (Table 21).

Despite the fairly modest changes in the acceleration factors, the sensitivity analysis suggested that the results for givinostat (EPIDYS/OLE) versus ECM (UK registry study) were less favourable for givinostat if acceleration factors derived from CINRG DHNS were used. Given the assumptions required when applying acceleration factors, and in assuming that those derived in ECM patients can be applied to givinostat patients, the EAG believe that this is a considerable source of uncertainty in the appraisal. Given that the true acceleration factor in the givinostat group is unknown, it is unclear which values are likely to be the most appropriate.

**Table 21: Unweighted hazard ratios for givinostat (EPIDYS/OLE) versus ECM (UK registry study), estimated using acceleration factors (AFT) derived from UK registry study (company base-case) and CINRG DHNS (company sensitivity analysis)**

| Outcome | UK registry derived AFT | CINRG DHNS derived AFT |
|---|---|---|
| Age at LOA | AFT: 0.67/0.66<br>**HR: 0.222 (0.153, 0.323)** | AFT: 0.73<br>**HR: 0.338 (0.232, 0.492)** |
| Age at NIV | AFT: 1.50<br>**HR: 0.228 (0.157, 0.332)** | AFT: 1.37<br>**HR: 0.338 (0.232, 0.492)** |
| Age at FVC <1L | AFT: 1.94<br>**HR: 0.233 (0.154, 0.353)** | AFT: 1.91<br>**HR: 0.254 (0.168, 0.382)** |

Abbreviations: 1L, one litre; AFT, acceleration factor; ECM, established clinical management; FVC, forced vital capacity; LOA, loss of ambulation; MAIC, Matched Adjusted Indirect Comparison; NIV, non-invasive ventilation.

### 3.4.5 Risk of bias assessment for uITC and MAIC (ROBINS-I)

Risk of bias assessments for the company studies, EPIDYS and OLE, were reported separately in sections 3.3.1.7 and 3.3.2.7. However, for the outcomes age at LOA, age at NIV, and age at FVC<1L, the EAG consider that these studies only partially inform the economic model via their contribution to the givinostat group in the uITC. The ECM group for the uITC is formed via the UK registry data.[18] Even if uITCs utilise data from randomised trials, they are not randomised comparisons but are observational comparisons which rely on assuming that all prognostic factors and effect modifiers are balanced across the groups. An appropriate assessment for the uITC should therefore use a tool for non-randomised studies. The EAG used the ROBINS-I tool to assess the risk of bias for age at LOA, age at NIV, and age at FVC<1L as estimated from the uITC and MAIC. The (adjusted robust SE) hazard ratios reported in EAG Table 16, Table 18 and Table 19 were considered in the assessment.

Overall risk of bias was judged to be critical for all three outcomes. Risk of bias due to confounding was judged to be serious for all three outcomes. Across the two data sources used in the uITC, there are several prognostic and modifying factors that could potentially induce bias but there is insufficient information on baseline characteristics to adequately assess comparability of the groups. The EAG consider that confounding was insufficiently controlled in the analysis, as groups were only matched on a single covariate (age at start of corticosteroids). The sensitivity analysis reported in EAG section 3.4.4.4 suggested that the results for givinostat (EPIDYS/OLE) versus ECM (UK registry study) were less favourable for givinostat if acceleration factors derived from CINRG DHNS were used. The EAG rated bias in the selection of the reported result as being at serious risk of bias and note concerns raised about selection of participants from EPIDYS/OLE/Study 43 in sections 3.3.2.2 and 3.4.2 of the EAG report. The EAG were not able to judge risk of bias for bias due to deviation from intended intervention or missing data, due to insufficient information being available to assess the domain. Bias in classification of intervention was judged to be low as intervention groups were defined by having been enrolled in the Company's givinostat studies or the UK registry data, for whom givinostat was not available.

**Key Issue 5: What is the impact of bias arising from the lack of randomised comparisons for key outcomes at longer-term timepoints?**

## 3.5 Conclusions of the clinical effectiveness section

### 3.5.1 Is there evidence of clinical effectiveness?

The company's submitted evidence is broadly in line with the final scope. However, the specified population is narrower and focuses on a subgroup of patients who are ambulant at initiation of givinostat. The estimates of clinical effectiveness in the CS are based on two studies, the company's RCT (EPIDYS) and longer term extension study (OLE). For the primary outcome, (mean change in the time taken to complete a 4SC between baseline and 18 months, there is evidence of clinical effectiveness but, after adjusting for multiple testing, key secondary ambulatory outcomes did not reach conventional statistical significance. Within the context of the CS, which covers the overall population of EPIDYS not only Group A as per the 'target population' specified in original trial protocol, the EAG has some concerns about the risk of bias for 4SC. This was attributable to the potential for bias from selection of reported outcomes. Treatment-related adverse events were higher in the givinostat arm of EPIDYS than for placebo. However, adverse events leading to study withdrawal were low (3 patients [3%] in the givinostat group and zero in the placebo group). AEs leading to dose reduction occurred in 42 patients (36%) in the givinostat group and 1 (2%) patient in the placebo group.

DMD is a degenerative, progressive disease and the company stress the importance of considering clinical significance. A minimal clinically important difference (MCID) for 4SC is not given, the EAG agrees that a derived outcome of velocity difference in tasks per second is similar to that reported in the literature as clinically significant. However, the EAG is not

able to confirm that velocity difference in tasks per second was a pre-specified analysis for EPIDYS.

Longer term outcomes come from the OLE study, in which all included participants receive givinostat. The primary outcome in OLE is safety and the study was not powered for comparative analyses on ambulatory outcomes. However, exploratory analyses comparing participants in a 'delayed' givinostat group (the placebo group from EPIDYS) with a continuous 'givinostat' group were reported. The EAG note there was no evidence that the hazard ratio for age at LOA differed between the delayed and continuous givinostat groups.

Relative effect estimates from the two company studies are not used directly in the CS economic model. The EAG notes that the transition probabilities required by the company's preferred model cannot be directly informed by the primary outcome of EPIDYS (4SC). Consequently, estimates of relative effectiveness informing the economic model is based on non-randomised evidence, via an uITC and MAIC.

### 3.5.2 Are estimates that feed into the economic model reliable and appropriate to the scope?

The two company studies inform the givinostat 'arm' of the uITC and MAIC. To form an ECM group for the uITC, the company used data obtained from a retrospective case review of a UK registry study.[18] The EAG are concerned about the reliability of comparative treatment effects estimated from an uITC, due to the likelihood of imbalance between prognostic factors and effect modifiers between the givinostat and ECM sources of data (Section 3.4.3). The EAG rated uITC estimates for age at LOA, age at NIV and age at FVC <1L as being at a critical risk of bias.

The outcomes relating to clinical effectiveness that feed into the economic model are the median time-to-event times from extrapolated survival curves for age at LOA, age at NIV and age at FVC <1L, estimated from an uITC. These outcomes are not directly the same as the health states used in the model (Section 4.2.6), but are used because they are the endpoints reported in both EPIDYS/OLE and the UK registry study. Furthermore, the EAG have concerns regarding the way in which the clinical estimates (median time-to-event times from extrapolated survival curves) are applied in the model, since hazard ratios for givinostat versus ECM for *each* modelled outcome (age at LOA, age at NIV, age at FVC <1L) are applied to transition probabilities. These hazard ratios capture *exactly the same mechanism for the treatment effect* due to the way in which they are derived (from age at LOA in givinostat patients, using acceleration factors), and so applying them to all transition probabilities likely overstates the efficacy of givinostat.

### 3.5.3 Are the most appropriate estimates been selected to feed into the economic model?

A summary of key analytic choices for both the company and EAG's base case analyses are given in Table 22. The company uses the absence of long-term comparative data to justify the use of an uITC to estimate comparative treatment efficacy. The EAG highlight that Technical Support Document 18 (TSD18) states that "u*ITCs should only be used in the*

*absence of [a connected network] of randomised studies*" (p.6).[34] As follow-up in EPIDYS is relatively modest (18 months) compared to the OLE, the number of LOA events is too small for analysis. However, there is considerable randomised evidence available from other outcomes reported within EPIDYS for givinostat versus ECM (e.g. 4SC, NSAA, cumulative loss of function). An alternative approach would have been to use the randomised outcomes reported in EPIDYS as surrogates for the economic model outcomes, to ensure that the randomised treatment effect (balanced for prognostic factors) was extrapolated into the longer-term and carried through into the economic model.

**Table 22: Summary of key analytic choices for company and EAG base-case analyses**

| Analytic approach | Company base-case | EAG base-case | EAG justification |
|---|---|---|---|
| **Data source for comparative treatment efficacy** | uITC matched to UK registry study | uITC matched to CINRG DHNS | Prognostic factors and effect modifiers are more likely to be balanced with matching to CINRG DHNS (Section 3.4.2) |
| **Data source for natural history baseline** | UK registry study | UK registry study | Natural history baseline should be informed by a data source most similar to the target population |
| **Data source for givinostat efficacy** | Subset of patients from EPIDYS/OLE | All patients from EPIDYS/OLE | Selection of EPIDYS/OLE patients is post-hoc and may introduce selection bias (Section 3.4.2.1) |
| **Extrapolation of givinostat outcomes using acceleration factors to estimate age at NIV and age at FVC <1L** | Applies acceleration factors derived from UK registry study (ECM) to givinostat age at LOA | Does not require estimation of data for age at NIV or age at FVC <1L | Company clarification B.3 stated that "no treatment effect is assumed beyond loss of ambulation". Whilst delaying LOA will also impact the HR for age at NIV and age at FVC <1L, including HRs for these nested outcomes within the economic model double counts the effect on age at LOA and will overstate efficacy of givinostat (Section 3.4.3.1). |

Although the EAG have highlighted their strong preference for using the randomised data from EPIDYS to estimate comparative treatment efficacy rather than an uITC, within the analyses provided by the company the EAG believe the most plausible estimates of comparative treatment efficacy are the MAIC estimates matched to CINRG DHNS. Although

the UK registry study is likely to provide the most plausible natural history baseline, it is unsuitable for estimation of comparative treatment efficacy. The EAG consider this is due to the substantial likelihood that not all prognostic factors and effect modifiers are balanced between this study and EPIDYS/OLE.

### 3.5.4 Uncertainties regarding the reliability of the clinical effectiveness data

Use of an uITC requires assuming that all prognostic factors and effect modifiers are balanced between groups. The company's base-case MAIC only includes a single prognostic factor (age at corticosteroid initiation), due to the limited availability of baseline characteristics reported in the UK registry study. Furthermore, the impact of weighting differs markedly depending on which prognostic factors are included in the MAIC and on the choice of data source (Section 3.4.4.4.1). The likelihood of bias arising from imbalance in these therefore adds considerable uncertainty to clinical effectiveness estimates.

There is also considerable uncertainty about the longer-term outcomes (age at NIV, age at FVC <1L) included in the economic model. These are reasonably sensitive to:

- **The choice of acceleration factors (Section 3.4.4.4.2)**: The true values of these acceleration factors within the givinostat patients are unknown. Smaller values used for acceleration factors are expected to increase patients' transition through givinostat states in the economic model, relative to ECM.
- **The choice of model for extrapolation of time-to-event outcomes:** Given the immaturity of data, median time-to-event times were not reached for all outcomes. These were therefore estimated from extrapolated survival distributions, the choice of which introduces additional uncertainty.

# 4 COST EFFECTIVENESS

## 4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify previous cost-effectiveness analyses. The EAG appraised the SLR using the ROBIS tool[15] finding the review to be overall at low risk of bias. The ROBIS assessment is reported in Appendix 7 (Section 9.7).

The company's cost-effectiveness literature aimed to capture a range of economic evidence surrounding the treatment of DMD and its published cost-effectiveness analyses since 2014. The economic SLR's search strategy and inclusion/exclusion criteria were well considered and the review identified relevant evidence on the cost-effectiveness modelling of the disease area. This included the identification of 5 previous health economic models in the literature using a UK perspective. Four of the previous DMD models identified were developed for a UK HTA, either for NICE or the SMC. The company's model structure was heavily influenced by the Broomfield et al., (2024)[4] multi-state transition model based on the natural history of DMD. Of the previous models of DMD in the UK identified in the SLR, all except one were Markov models.

## 4.2 Summary and critique of the company's submitted economic evaluation by the EAG

### 4.2.1 NICE reference case checklist

Table 23 below summarises the EAG's comments on the CS, in relation to the NICE reference case. The EAG highlights issues where the company's submission deviates from the NICE reference case or where the EAG has highlighted a potential issue.

**Table 23: NICE reference case checklist**

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| Perspective on outcomes | All direct health effects, whether for patients or, when relevant, carers | Not consistent with the reference case.<br><br>Utilities and healthcare costs do not distinguish between patients with no HTMF with full ventilation and patients with no HTMF and only night ventilation.<br><br>Healthcare costs due tertiary care and medical aids not captured by submitted model. |

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| | | Increments and decrements (or disutilities) included for caregivers relative to the midway health state. These are applied to the incremental life years in the givinostat arm only. The company assumes no caregiver QALYs are accrued in the ECM arm. |
| Perspective on costs | NHS and PSS | Consistent with the NICE reference case |
| Type of economic evaluation | Cost–utility analysis with fully incremental analysis | Consistent with the NICE reference case |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | Consistent with the NICE reference case with lifetime horizon used. |
| Synthesis of evidence on health effects | Based on systematic review | Consistent with NICE reference case a systematic review was conducted.<br><br>However, identified studies were used to estimate effect of givinostat relative to ECM using an unanchored matching adjusted indirect comparison. The EAG considers this uITC to be at critical risk of bias. (Section 3.4.5). |
| Measuring and valuing health effects | Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults. | Health effects are expressed in QALYs. However, EQ-5D not consistently used for utilities.<br><br>The observational study Audhya et al. 2023 chosen to source patient utilities for the company's base case is not representative of the UK population and the EuroQol 5 dimensions 5 level questionnaire (EQ-5D-5L) is not recommended for decision making.[42]<br><br>Caregiver utilities derived from vignette study which was used TTO rather than EQ-5D.[43] |

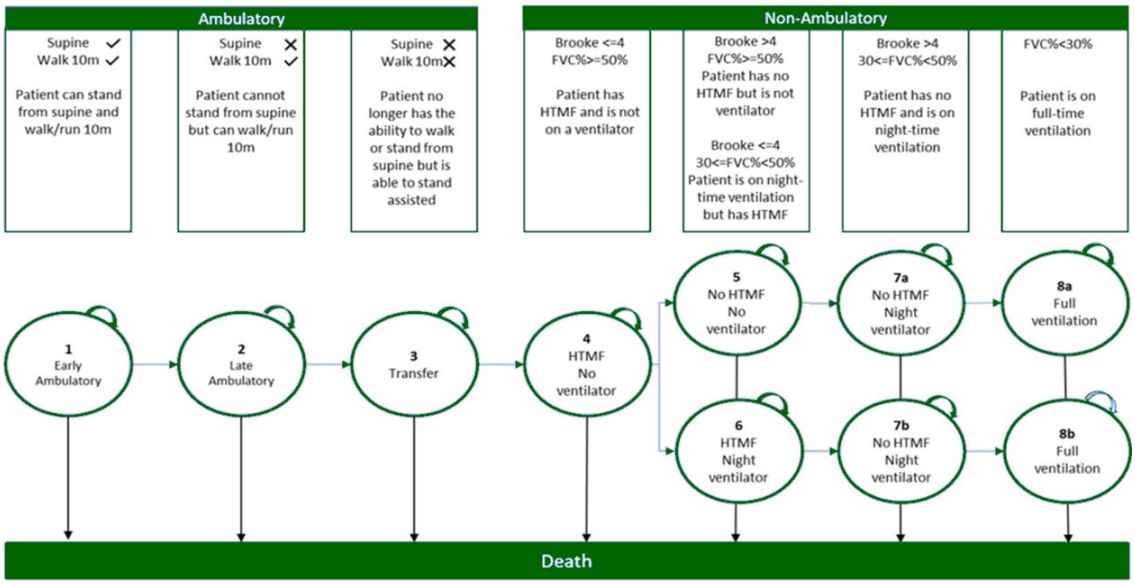
| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| Source of data for measurement of health-related quality of life | Reported directly by patients and/or carers | The company's approach does not follow the hierarchy of preferred HRQoL methods as per NICE reference case.[28]<br><br>Despite having Health-related quality of life (HRQoL) PedsQL available in the OLE study, and PODCI in the EPIDYS study, the company relied solely on HRQoL data from external sources Audhya et al. 2023.[42] |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population | Health state utilities from US study Audhya et al. 2023.[42]<br><br>Spinal fusion disutility from Matza 2014 which mixed UK and Canadian patients together.[44] In this study, only 126/187 were in the UK.<br><br>AEs disutility for diarrhoea (with abdominal pain and upper abdominal pain assumed equivalent) from UK study Sullivan 2011.[45] AE disutility for vomiting from Japanese study Hagiwara 2018.[46]<br><br>Caregiver utilities from UK-based vignette study.[43] |
| Equity considerations | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Consistent with the NICE reference case. Carer HRQoL included. |
| Evidence on resource use and costs | Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS | Model uses NHS and PSS resources and is valued at prices relevant to the NHS and PSS. |
| Discounting | The same annual rate for both costs and health effects (currently 3.5%) | Costs discounted at 3.5% per annum, aligned with NICE reference case.<br><br>Outcomes are discounted at 3.5% up to 30 years and 1.5% beyond 30 years, so not aligned with the reference case. |

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|

PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

### 4.2.2 Model structure

**Figure 7: Model structure (CS, Fig. 34)***




*Abbreviations: FVC, forced vital capacity; HTMF, hand-to-mouth function; m, metres.

The company submission model structure is illustrated in Figure 7. This includes a description of state definitions and allowed transitions. The structure is that of the Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis) natural history model (NHM), as described in Broomfield 2024.[4] Project HERCULES is led by the charity Duchenne UK. The Brooke and FVC score capture the key determinants of utilities and cost in the non-ambulatory states.

The HERCULES structure was used in the vamorolone appraisal in DMD but was unavailable at the time of the ataluren appraisal.[2, 3] In the vamorolone appraisal, both the EAG and committee found the model structure appropriate for decision making. The ataluren model captured LOA as the key clinical milestone. The EAG and committee found the model to be appropriate but EAG critiqued excluding the transfer health state and committee critiqued for not differentiating between early and late ambulatory health states. They do not appear to critique it for having a smaller number of non-ambulatory health states. However, these limitations of the ataluren model are addressed by the HERCULES structure.

Attempts by the company to address limited data at later stages is discussed in Section 4.2.6 below. The EAG notes that the number of ambulatory states in the present model remains limited.

Health states include impact on HRQoL of informal caregivers. The company provides justification for this impact through literature and clinical opinion. It is also aligned with the committee conclusion on the NICE appraisal of vamorolone for treating DMD (TA1031).[3] The Committee for the NICE appraisal of ataluren considered the impact on caregivers in its decision making in a qualitative way.[2]

The model uses a one-month cycle length with half-cycle correction.
A key issue with following the HERCULES model structure is that neither the primary outcome of EPIDYS (i.e., mean change in the time taken to complete a standard four-stair climb between baseline and 18 months) nor any of the other outcomes collected during the randomised phase of the trial, directly inform transition rates. This leads the model to rely on a MAIC approach which the EAG considers to be at critical risk of bias (Section 3.4). The EAG suggests an alternative model structure using continuous outcomes as a health state (e.g., categories of time to complete the four-stair climb) or event (e.g., is the event a specific increase in time to complete the climb). The EAG considers that this would match the EPIDYS trial primary outcome.

However, in addition to HERCULES being previously accepted and informed by clinical opinion and literature reviews, the EAG notes that there are two reasons for not building a model on the EPIDYS primary outcome. Firstly, the EAG does not consider it straightforward to represent the continuous outcome as a health or event nor to estimate utilities for these events. Secondly, if the placebo arm of EPIDYS is not accepted as representative of baseline natural history, an external source of data to inform baseline natural history would be needed (see Section 3.3.1.3). This would be a challenge as EAG clinical advice indicated that the primary outcome of EPIDYS (4SC) is less frequently measured in clinical practice settings due to its requiring four steps for measurement. The EAG therefore considers the use of HERCULES to be a good conceptual representation of DMD and expected to better link to available data from external sources of data.

Loss of ambulation due to fractures was identified as an issue in the appraisal of vamorolone in TA1031 and subsequently added to the model following first committee meeting. This is relevant to the givinostat appraisal the CEM is missing the modelling of fractures despite the evidence from EPIDYS and OLE as discussed section 4.2.7. A study by Yildiz et al 2020 reported that 36.4% of those with a long bone fracture lost ambulation permanently.[47]

### 4.2.3 Population

The model considers people with DMD six years of age and older who are ambulant when they initiate treatment. Weight, height, and body surface area (BSA) for boys aged 6–18 years were sourced from the Royal College of Paediatrics and Child Health data (CS, Table 38).[48]

#### *4.2.3.1 Subgroups*

No subgroups were considered.

### 4.2.4 Interventions and comparators

The intervention is givinostat. Givinostat is administered orally twice daily with food with (CS, Table 42). Givinostat is given in addition to Established Clinical Management (ECM).

The sole comparator is ECM. The company states that despite not being indicated for the treatment of DMD in the UK, oral corticosteroids, including prednisone or deflazacort, are the ECM for DMD, as per the International DMD Care Considerations guidelines and UK clinical feedback from clinicians attending the company's June 2024 HTA advisory board.[49-51] EAG clinicians agreed with the CS (See sections 2.1 and 2.2).

The distribution of corticosteroids and associated dosing schedules comprising ECM are informed by the EPIDYS data (CS, Table 17); following the BNF, prednisone is assumed administered orally as 0.75 mg/kg daily and deflazacort administered orally as 0.90 mg/kg daily.[52, 53] In terms of dosing schedule, as per EPIDYS, 82.1% are assumed to receive a daily schedule and 17.9% are assumed to receive an intermittent schedule reflecting 10-days on and 10-days off i.e., half the dose of those patients receiving the daily schedule.

### 4.2.5 Perspective, time horizon and discounting

An NHS and PSS perspective and lifetime horizon are used, in line with the NICE reference case. Discounting of costs is at 3.5% per annum. However, discounting of outcomes is at 3.5% up to 30 years and 1.5% beyond 30 years, so not aligned with the NICE reference case. EAG clinical advice was that it was unknown whether givinostat would confer a longer term benefit, including beyond discontinuation of givinostat. Clinical advisers noted that there may be a residual effect if givinostat prevented fibrosis so that by the age of 16 patients would have less fibrosis than if they had not been on it, which might protect them after they discontinue treatment.

### 4.2.6 Treatment effectiveness and extrapolation

The primary data source informing transitions in the HERCULES NHM is the Critical Path Institute (C-Path) Duchenne Regulatory Science Consortium (D-RSC). This consists of data from 11 international data sources and 4467 transitions between states. This provides the transitions between states "(1) Early Ambulatory", "(2) Late Ambulatory", and "(3) Transfer".

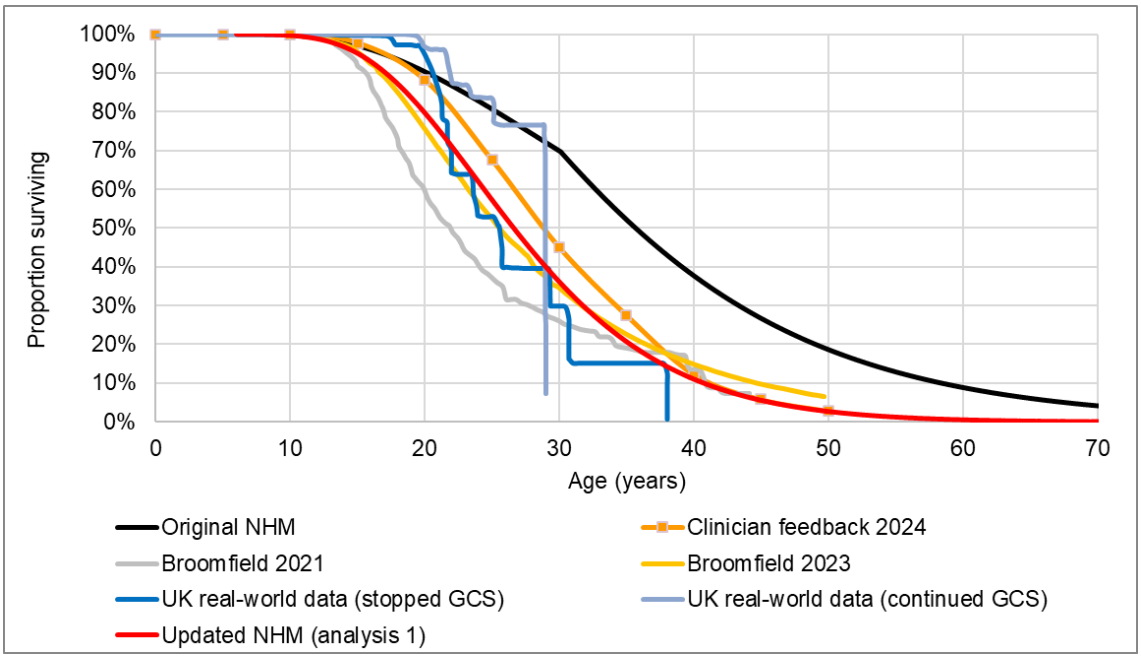
D-RSC data were not available for model transitions from state “(3) Transfer” to the HTMF states, so elicitation was used instead. Due to limited data from D-RSC, elicitation was also used to inform transitions between “(4) HTMF, no ventilation”, “(5) no HTMF, no ventilation”, and “(6) HTMF, nighttime ventilation” health states. The elicitation included views from 4 caregivers involved in HERCULES, online views from 20 UK stakeholders (including healthcare practitioners, parents, and caregivers), and 20 further UK responses from Duchenne UK.

No mortality data were available from D-RSC so an SLR and (piecewise constant on reconstructed IPD from KM) meta-analysis were conducted on mortality.

Transition intensities informed by D-RSC were estimated using the 'msm' package in R.[54] This package restricted transitions to only those between states. The EAG views this acceptable given the short cycle length (1 month) of the Markov model.

The company found that mean age in states 8a and 8b (i.e., full ventilation states) are higher than expected. This overestimation is illustrated in Figure 8. This compares NHM survival extrapolations to a meta-analysis of published survival data reported in Broomfield et al. 2021, survival estimates from the UK CPRD cohort study reported in Broomfield et al. 2023, survival estimates from unpublished data reflecting outcomes for N=156 patients treated with corticosteroids across centres in London, Newcastle, and Oxford (UK real-world data), and landmark estimates predicted by the company's April 2024 advisory board.[4, 55-58] Overestimated survival is a recognised problem with HERCULES in the vamorolone NICE appraisal (TA1031) and justified the company to explore updates to transition rates.

**Figure 8: A comparison of survival from the updated NHM (analysis 1) with external sources and the published NHM (CS, Fig. 36)**




The company conducted two analyses to update the NHM using hazard ratios estimated by the SOLVER tool in Microsoft Excel. SOLVER minimises differences between the model predictions and reported data by varying hazard ratios applied to transition probabilities.

In analysis 1, SOLVER was used to estimate HR for death from 8a and 8b to force the model to match the proportion alive at 50 years based on UK clinical experts (i.e., 2.8%). This returned a HR of 8.3 for transitions from health states (8a) and (8b) to death. Results are illustrated in Figure 8 and tabulated in Table 24. While the original NHM matches UK real world data for patients who continued corticosteroids, analysis 1 matches patients who stopped corticosteroid, which is the relevant group for this appraisal. It is precisely aligned with the 50-year survival data.

Analysis 2 also aligned with the 50-year survival estimate with transitions to death from 8a and 8b but adds calibration to median age at loss of ambulation (as reported by UK real world data and provided in Table 25) by applying an HR to transitions from (1) to (2), (2) to (3), and (3) to (4). This estimated a HR of 1.6 for transitions from (1) to (2), (2) to (3), and (3) to (4) and 3.8 for transitions from health states (8a) and (8b) to death. Results are illustrated in Figure 9 and tabulated in Table 24. Analysis 2 again matches patients who stopped corticosteroid and is precisely aligned with 50-year survival data. It furthermore better matches reported milestones for age at loss of ambulation than analysis 1 and the original NHM (Table 24).

In general, it underestimates survival compared to clinical opinion at ages 15, 20, 25, 30, and 35, only matching at 40 and 50 years. It also consistently underestimates the age of starting ventilation, starting full time ventilation and death compared to UK real world data[58]. This could overestimate the benefit of givinostat.

**Figure 9: A comparison of survival from the updated NHM (analysis 2) with external sources and the published NHM (CS, Fig. 37)**

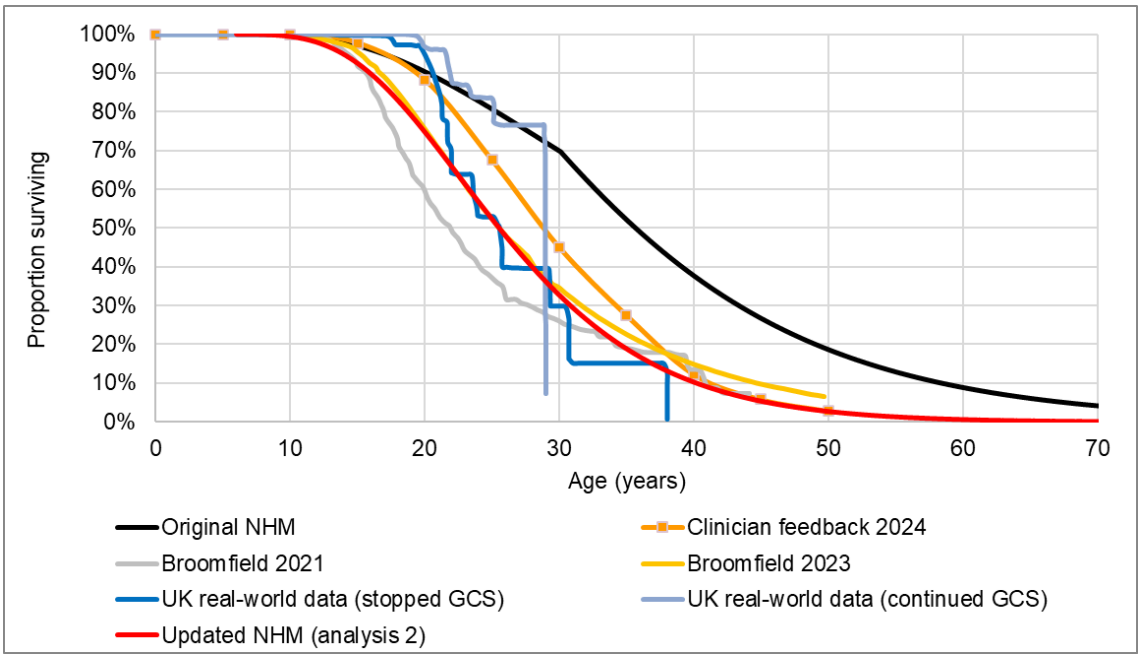


**Table 24: A comparison of survival from the updated NHM (analysis 2) with external sources and the published NHM (CS, Table 45 and 46)**

| | Updated NHM (analysis 1) | Updated NHM (analysis 2) | Published NHM[4] | Broom-field 2021[57] | Broom-field 2023[56] | Clinical feedback 2024[55] | UK real-world data (stopped GCS)[55] | UK real-world data (continued GCS) | Weighted UK real-world data |
|---|---|---|---|---|---|---|---|---|---|
| Median | 26.6 | 25.5 | 35.6 | 21.8 | 25.4 | NA | 25.5 | 28.9 | 27.8 |
| | **% surviving at (age):** | | | | | | | | |
| 10 | 99.7% | 99.4% | 99.7% | 99.9% | 100.0 % | 100.0% | 100.0% | 100.0% | 100.0% |
| 20 | 79.7% | 74.8% | 90.3% | 60.7% | 76.1% | 88.2% | 97.0% | 97.0% | 97.0% |
| 30 | 36.1% | 32.7% | 69.9% | 26.0% | 34.6% | 45.0% | 29.8% | 7.3%** | 14.5% |
| 40 | 11.2% | 10.4% | 37.8% | 13.6% | 15.3% | 12.3% | 0.6%* | NA | 0.6% |
| 50 | 2.8% | 2.8% | 18.7% | 7.3% | 6.4% | 2.8% | NA | NA | NA |

Abbreviations: GCS, glucocorticosteroids; NA, not available; NHM, natural history model
*% surviving based on last available data point at age 38. **% surviving based on last available data point at age 29.

**Table 25: Comparison of age milestones from published NHM, updated NHMs, and UK real-world data (Company Submission Table 47)**

| Median age at: (in years) | Updated NHM (analysis 1) | Updated NHM (analysis 2) | UK real-world data[55] | Published NHM[4] |
|---|---|---|---|---|
| Unable to stand from supine | 10.2 | 8.7 | NA | 10.2 |
| Loss of ambulation | 15.5 | 12.1 | 12.1 | 15.5 |
| Starting ventilation | 19.6 | 16.0 | 18.1 | 19.6 |
| Starting full time ventilation | 23.9 | 20.3 | 20.5 | 23.9 |
| Death | 26.6 | 25.5 | 28.0 | 35.6 |

Abbreviations: NA, not available; NHM, natural history model.

We explore this further below but an issue with using SOLVER, rather than statistical estimation or calibration methods, is that no standard deviation or uncertainty is provided for the estimated hazard ratios. Furthermore, the only 'data' on survival at 50 years is clinical advice received by the company at its advisory board.[55]

Treatment effects were indirectly informed by the unanchored MAIC HR (critiqued in Section 3.4). The company did not use these hazard ratios directly as the transitions did not align with the analysed outcomes. Instead, the company fit parametric survival models to the MAIC-weighted givinostat curves for loss of ambulation, age at non-invasive ventilation, and age at FVC<1L. They then used SOLVER to fit HRs to the CEM transition rates to align the CEM predictions with these three parametric curves. As givinostat is not anticipated to directly impact the probability of dying, HRs of one are applied to all transitions to death. The estimated hazard ratios are provided in Table 26.

**Table 26: HRs applied to health state transitions in the CEM to represent benefit of givinostat over ECM (Company Submission Table 51)**

| Health state transitions | HR |
|---|---|
| To state 2 - Late ambulatory | 0.51 |
| To state 3 - Transfer | 0.51 |
| To state 4 - HTMF, no ventilation | 0.51 |
| To state 5 - No HTMF, no ventilation | 0.39 |
| To state 7a - No HTMF, night-time ventilation | 0.39 |
| To state 8a - Full time ventilation | 0.46 |
| To state 6 - HTMF, night-time ventilation | 0.39 |
| To state 7b - No HTMF, night-time ventilation | 0.46 |
| To state 8b - Full time ventilation | 0.46 |
| **Mortality transitions** | **HR** |
| From state 1 - Early ambulatory | 1.00 |
| From state 2 - Late ambulatory | 1.00 |
| From state 3 - Transfer | 1.00 |
| From state 4 - HTMF, no ventilation | 1.00 |
| From state 5 - No HTMF, no ventilation | 1.00 |
| From state 7a - No HTMF, night-time ventilation | 1.00 |
| From state 8a - Full time ventilation | 1.00 |
| From state 6 - HTMF, night-time ventilation | 1.00 |
| From state 7b - No HTMF, night-time ventilation | 1.00 |
| From state 8b - Full time ventilation | 1.00 |

Abbreviations: CEM, cost-effectiveness model; HR, hazard ratio; HTMF, hand-to-mouth function.

While no direct treatment effect for givinostat is assumed beyond the LOA milestone, the impact of delaying LOA confers a benefit of lower transitions between later states. Note that the assumed hazard ratios on later transitions make the model invalid for assessing cost-effectiveness in non-ambulant populations as they would appear to benefit regardless of age of LOA.

The EAG highlight that the HRs used in the model relate to outcomes that are nested within each other. Age at FVC <1L incorporates both time to LOA and time to NIV, and age at NIV

incorporates time to LOA. When analysed independently it is therefore reasonable (albeit with the extensive limitations detailed in Section 3.4) to assume the use of acceleration factors in this way. However, the HRs estimated for each of the outcomes capture *exactly the same mechanism for the treatment effect* due to the way in which they are derived (from age at LOA in givinostat patients, using acceleration factors). Therefore, applying multiple HRs in the economic model that repeatedly capture the same mechanism is likely to double count the benefits of givinostat. The EAG explored the impact of this in scenario analyses (Section 6.1).

Please see Section 3.4 for issues with the comparator dataset used for the MAIC and the assumptions on acceleration factors. These issues also apply to the MAIC weighted curves used for the CEM.

We note again the issue that SOLVER estimated hazard ratios have no uncertainty estimates. A more formal approach such as maximum likelihood estimation or Bayesian estimation would have been possible. The company could have written a likelihood based on the NHM transition probabilities, and givinostat hazard ratios, with 'data' from the MAIC-weighted givinostat data for median time to loss of ambulation, non-invasive ventilation, and FVC<1L. Maximising this likelihood would give estimated HRs and error estimates.

With a much longer follow-up within the randomised phase of EPIDYS, the company could have used the RCT to estimate effect of givinostat on the model outcomes (i.e., age at LOA, age at NIV and age at FVC<1L) vs placebo and then applied these hazard ratios to the ECM natural history model. This would not use the primary outcome of EPIDYS but would avoid an unanchored MAIC. However, collection of sufficient data for these longer-term outcomes would not have been possible within a realistic time frame. An alternative approach would have been to use the outcomes reported in the RCT as surrogates for the economic model outcomes, to ensure that the randomised treatment effect (balanced for prognostic factors) was carried through into the model.

Another issue is that treatment effect against placebo may overestimate the effect against ECM. However, what EPIDYS really compared was givinostat + ECM vs placebo + ECM (patients continued receiving their prescribed corticosteroid regimen which is the main component of ECM other than non-pharmacological interventions, which they were probably also receiving). This relates again to the key issue of a mismatch between the NHM and EPIDYS trial, as noted when describing the model structure in Section 4.2.2.

### 4.2.7 Health related quality of life

The company's model is reliant on patient utilities sourced from observational studies as they deemed it infeasible to incorporate patient reported outcomes from the EPIDYS and OLE studies. The Paediatric Outcomes Data Collection Instrument (PODCI) was administered in the EPIDYS study and the mean change in the Standardised Global Function scale (one of the five subscales) was reported in in CS, section B.2.6.3. The Paediatric Quality of Life

Inventory (PedsQL) and 36-item Short Form Health Survey (SF-36) were administered in the OLE study but not reported in detail in CS, section B.2.6.6. (EAG report 3.3.1.6 and 3.3.2.5)

In clarification question B10, the EAG sought to explore scenarios incorporating trial-based utilities, achieved by mapping of Peds-QL to EQ-5D. The company's response was to reiterate the reasons stated in the CS for not undertaking these calculations in order not to introduce additional uncertainty for a number of reasons. The OLE study has increasing degree of missing values at later follow-up times. The mapping studies' participant characteristics are incompatible with the target population and health states of the economic model. Furthermore, in clarification B11, the EAG suggested mapping of PODCI to EQ-5D by Posner et al. 2024[59] in response to claims a mapping algorithm was not available or, alternatively, mapping PODCI to PedsQL (McDonald et al. 2013).[60] To this the company determined this was not feasible as the algorithm was not publicly available. In addition, mapping PODCI to PedsQL was undesirable as it would compound uncertainty.

The observational study chosen to source patient utilities for the company's base case is not representative of the UK population and the EuroQol 5 dimensions 5 level questionnaire (EQ-5D-5L) is not recommended for decision making.[42] This was a small survey of n=63 individuals aged 12-40 with DMD in US. Respondents were classified into 13 severity health states using upper limb function, ventilation status and cardiomyopathy. Although broadly similar to the 8 HERCULES health states used in their Markov model, investigators did not assess Time to stand from supine, Time to walk/run 10 m and the North Star Ambulatory Assessment (NSAA). Utility values for the health states were derived from the EQ-5D-5L using a US tariff value set rather than a UK value set.

The observational studies relevant to decision making in the UK report Health Related Quality of life on the DMD-QoL, PedsQL and HUI scales. The NICE methods guide directs users to source EQ-5D data from literature if not available from clinical trials. The EAG notes the apparent lack of literature with EQ-5D data suitable for decision making in the UK identified in the company's SLR. The two studies explored in scenarios by the company have also been used in TA1031,[3] with the exception of EQ-5D values from the Landfelt studies were made available more recently and presented in place of the HUI values used in the CEM. The committee and EAG noted the limitations of the studies and preferred the burden of illness (BOI) study informed by a Delphi panel, which measured quality of life for patients and caregivers in the UK using EQ-5D as part of Project HERCULES closely matching the natural history model.[6, 61] The EAG follows this recommendation to use the BOI study to inform health state utilities in the givinostat cost-effectiveness model as it is set in the UK and uses EQ-5D.

**Table 27: EQ-5D HRQoL of patients by Health State, BOI Study, Landfeldt et al 2023 (TA 1031)**

| | BOI study | | Landfeldt et al 2023[62] |
|---|---|---|---|
| Early ambulatory | 0.7 | (0.63-0.77) | 0.65 |

| | | | |
|---|---|---|---|
| Late ambulatory | 0.49 | (0.43-0.55) | 0.49 |
| Transfer | 0.38 | (0.35-0.41) | |
| HTMF, no ventilation | 0.54 | (0.51-0.57) | 0.31 |
| No HTMF, no ventilation | 0.51 | (0.48-0.54) | |
| HTMF, night-time ventilation | 0.53 | (0.50-0.56) | 0.26 |
| No HTMF, night-time ventilation | 0.52 | (0.50-0.54) | |
| Full-time ventilation | 0.33 | (0.31-0.35) | |
| Company estimated utility for Full-time ventilation using 0.39x multiplier | 0.13 | | 0.06 |

In clarification question B12, the EAG inquired as to the rationale behind the company modelling care giver quality of life for the treatment group using a vignette study. The company referred to a publication[63] which discusses the inappropriate use of EQ-5D for DMD .[64]The EAG notes while any vignette study maybe accepted as a source of utilities, the NICE methods guide stipulates evidence should be derived from a synthesis of peer-reviewed literature to make the case for the inappropriate use of EQ-5D. Furthermore, the EAG notes the carer quality of life from the BOI study supplemented with values from Landfeldt 2017 for health states 5,6,7 was accepted for decision making on the vamorolone appraisal. The EAG preferred BOI caregiver utility decrements from TA1031, presented in Table 28 alongside caregiver utility decrements derived from the same BOI study used in the CEM.

**Table 28: Caregiver Health Related Quality of Life increments or decrements by health state accepted for decision making in vamorolone appraisal (TA1031) and CEM Scenario**

| Health States | EAG preferred BOI values | BOI values applied in CEM |
|---|---|---|
| 1 - Early ambulatory | 0 | -0.203 |
| 2 - Late ambulatory | -0.14 | -0.253 |
| 3 - Transfer | -0.07 | -0.343 |
| 4 - HTMF, no ventilation | 0.08 | -0.363 |
| 5 - No HTMF, no ventilation | 0.23 | -0.423 |
| 6 - HTMF, night-time ventilation | 0.23 | -0.383 |
| 7 - No HTMF, night-time ventilation | 0.26 | -0.413 |
| 8 - Full time ventilation | -0.19 | -0.443 |
| 9 - Death (bereavement - all deaths) | - | -0.923 |

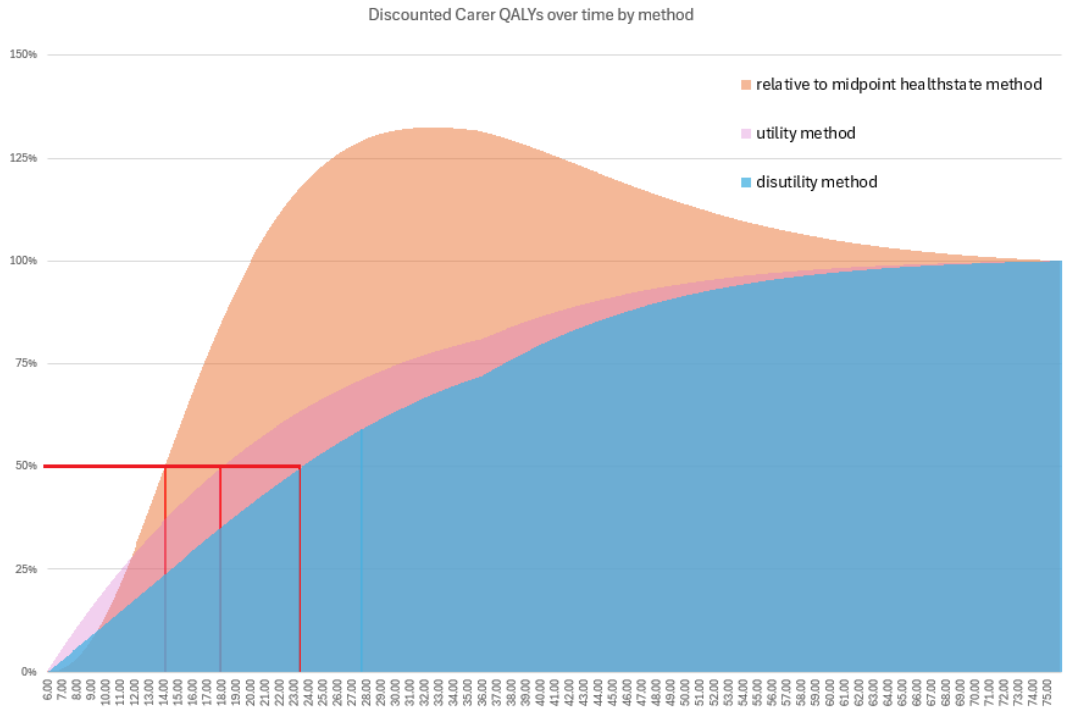
CEM Company's Economic Model

The EAG updated the approach in modelling the quality of life of caregivers. The company did not calculate caregiver QALYs for the ECM arm and the EAG do not consider their justification for not doing so in response to clarification B13 to be reasonable. The EAG recommends a method where the quality of life is accounted for on both ECM and givinostat arms, as otherwise an imbalance is created. The company apply a bereavement disutility for dead patients but in response to clarification B.14 do not provide sufficient evidence. The EAG did not include the utility decrement for dead patients, otherwise referred to as the bereavement disutility in the corrected base case.

The EAG prefers to account for caregiver quality of life using the disutility decrements method and the values presented in Table 28 as was discussed and accepted in TA1031. Although the company present three alternate methods accounting for caregiver HRQoL, in clarification response B15 they find substantial uncertainty concerning the choice of an appropriate method in terms of how QALYs are accrued over time. EAG analysis is presented in Figure 10 to illustrate the impact of different methods; The company's base case uses the carer utilities relative to midway health state method (orange curve), notable are the following features:

- 50% (red vertical line) of total carer utilities are accrued by the age of 14 in comparison to 18 using the utility method and 24 if using the disutility method (blue curve).
- Excess QALYs (over 100%) are accrued in comparison to the utility / disutility methods.
- QALYs after a patient's death due to the bereavement disutility (not shown on chart) are multiple times greater than the QALYS in the alive health states in comparison to the disutility method.

**Figure 10 comparison of methods for accruing carer HRQoL over time in CEM**




The CEM assumes an average of 2 caregivers per patient (alive or dead) are affected. The EAG prefers modelling an increasing caregiver burden as in the vamorolone appraisal in TA1031, the number of carers on the were assumed to be 1 for ambulatory health states (1-3), and 2 caregivers for non-ambulatory health states (4-8).

While the CS acknowledges the need to monitor DMD related comorbidities and treatment related adverse events (TRAEs), only spinal surgery was included in the model. The company did not add other TRAEs for bone health included spinal, vertebral or other fractures when asked about monitoring of bone health in clarification question B8. The EAG notes 0.8% of patients in the EPIDYS study participants (Table 33 of CS) experienced Spinal fracture. On the OLE study 26.1% of boys experienced falls classed as a Treatment Emergent Adverse Event (TEAE) and 5.8% of boys experienced femur fractures, the most frequent Serious Adverse Event (SAE), as documented in CS, Appendix F. Other DMD related comorbidities and adverse events known due to the use of corticosteroids were captured in the vamorolone appraisal including weight gain, cataracts behavioural issues and growth stunting were not included in the CEM.

The EAG notes, the severity modifier due to QALY shortfall does not apply carer QALYs in agreement with the EAG on the vamorolone appraisal and as detailed in section 6, p.100 of the ERG vamorolone report (TA1031 committee papers). In addition, this guidance is explained by the QALY shortfall guide TSD 23.[65] We illustrate this in Table 29 (below) with an example of a balanced approach where severity modifier is (i). incorrectly applied to both the incremental patient and carer QALYs, and (ii). correctly applied to incremental patient QALYs only.

**Table 29: Example of total incremental QALYs with and without severity modifier (1.7x) applied to incremental carer QALYs.**

| Severity Modifier applied to | ECM QALYs | | Treatment QALYs | | Incremental QALYs | | Total Incremental QALYs w/ severity modifier |
|---|---|---|---|---|---|---|---|
| | Patient | Carer | Patient | Carer | Patient | Carer | |
| i. Incremental Patient & Carer QALYs (incorrect) | 6.2 | 17 | 10.2 | 26.2 | 4.0 | 9.2 | 13.2*1.7 = 22.4 |
| ii. Incremental Patient QALYs (correct) | 6.2 | 17 | 10.2 | 26.2 | 4.0 | 9.2 | (4.0*1.7) + 9.2 = 16 |

### 4.2.8 Resources and costs

In clarification B8 the EAG sought for administration and monitoring costs to reflect the differences between givinostat and ECM as we received clinical advice with the expectation to administer treatment and monitoring in tertiary care. In addition, there is an expectation of routine monitoring of bone health and endocrinology. In response to B8 the company acknowledged the SPC for givinostat recommends regular monitoring of platelet counts and triglycerides for the purposes of adjusting the dosage. The company explore a scenario with non-consultant led monitoring. The EAG explore a scenario with consultant led monitoring appointments with the assumption that a specialist consultant will be involved in monitoring the patients as detailed in Table 30.

The company did not expect differences in treatment administration costs between givinostat and ECM as was the case in vamorolone appraisal (TA1031) and the ataluren appraisal (HST22). Furthermore, we note other routine costs related to the bone health and endocrinology of DMD patients were not modelled. The question remains on the role of tertiary care in treatment administration and monitoring; are 6 months routine visits sufficient to cover treatment administration and monitoring? Although the EAG in HST22 did not critique the company's assumptions, we note clinical experts detailing the role of specialty NM centres as essential in supporting treatment administration and monitoring.

**Table 30: Monitoring costs included in CEM as scenario in response to clarification B8 and EAG Scenario using alternative costs**

| | Company‡ | EAG* | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6+ |
|---|---|---|---|---|---|---|---|---|
| Blood counts | £2.00 | £2.00 | 2 | 2 | 1 | 0 | 0 | 0.33 |
| Triglycerides | £2.00 | £2.00 | 1 | 0 | 1 | 0 | 0 | 0.17 |
| First appointment | £208.00 | £630.33 | 1 | 0 | 0 | 0 | 0 | 0 |
| Follow-up appointment | £208.00 | £253.12 | 1 | 2 | 1 | 0 | 0 | 0.33 |
| Total (Company scenario) | | | £422.0 | £420.0 | £212.0 | £0 | £0 | £70.33 |
| Total (EAG scenario) | | | £889.5 | £510.3 | £257.1 | £0 | £0 | £84.53 |

*‡NCL 420 Paediatric Service. Non-admitted F2F attendance, follow-up.*
**CL 421 Paediatric Neurology Service Paediatric Neurology Service First (WF01B) & Follow-up (WF01C)*

In clarification B9 the EAG sought to include health state costs not captured by literature to which the company acknowledged the limitations with health state costs not capturing tertiary care and medical aid costs. The company have acknowledged this issue and proposed applying a multiplier to account for costs associated with non-medical community services, medical aids and devices. There are two issues with this approach; (i) the study by Morgan et al used to source the direct medical costs, although applicable to the UK, does not align with the severity states for the model. (ii) The multiplier derived by the company does not help in estimating tertiary care costs (not captured by the observational studies) and was based on additional costs that include non-medical community services (i.e., non-NHS or PSS costs) which may or may not align with the NICE reference case.

The committee for TA1031 accepted the BOI study (values in Table 31 below) and the EAG preferred BOI over the Landfeldt study because it aligns better with the severity health states of the HERCULES Natural History model. The EAG estimated an alternative multiplier excluding the non-medical community services, to be 0.57x rather than the 2.05x estimated by company and applied this to the BOI direct medical costs preferred in TA1031. However, the EAG notes a drawback to this approach being the lack of differentiation between the severity states.

Treatment related adverse events, DMD related comorbidities and adverse events of special interest known due to the use of corticosteroids not captured in the company's model were discussed in 4.2.7.

The treatment dosage in the model appears to follow what is described in Table 46 of CS, Appendix M, but the EAG did not verify if this is equivalent to dosing tables in the UK SPC. The company notes, in section B.2.3.1 of the CS, that the strength of givinostat is expressed as "givinostat hydrochloride monohydrate" in EPIDYS, whereas it is expressed as "givinostat free base" in the UK summary of product characteristics, at the dose "8.86mg/mL oral suspension".[66] The company reports that 10 mg/ml givinostat hydrochloride monohydrate is equivalent to 8.86 mg/ml givinostat free base.

**Table 31: Direct medical and non-medical costs (with/ without) the multiplier applied for non-medical community services, aids, devices, and investments**

| Health states, N | Morgan et al (CEM) | | BOI (CEM) | | BOI study (TA 1031 Committee preferred) | |
|---|---|---|---|---|---|---|
| | Direct medical | Multiplier applied to direct medical | Direct medical | Non-medical | Direct medical | Multiplier (0.57x) applied to direct medical |
| Early ambulatory | £3,298 | £10,068 | £5,592 | £12,398 | £7,680 | £12,058 |
| Late ambulatory | | | £3,097 | £666 | £3,391 | £5,324 |
| 3 Transfer | | | £3,592 | £17,911 | £3,625 | £5,691 |
| 4 HTMF, no ventilation | £6,681 | £20,397 | £2,370 | £38,539 | £2,472 | £3,881 |
| 5 HTMF, night ventilation | | | £3,349 | £45,007 | £3,507 | £5,506 |
| 6 No HTMF, no ventilation | £9,843 | £30,049 | £8,430 | £44,142 | £7,837 | £12,304 |
| 7a No HTMF, 7b night ventilation | | | £7,978 | £47,186 | £7,771 | £12,200 |
| 8a, 8b Full ventilation | | | £10,506 | £23,555 | £12,579 | £19,749 |
| Company estimated costs for 8a, 8b Full ventilation using 1.3x multiplier | £12,961.6 | | £13,835.5 | | | |

# 5 COST EFFECTIVENESS RESULTS

## 5.1 Company's cost effectiveness results

A summary of the company's base case was presented and discussed in section 4 and was not updated in response to clarification questions, rather sensitivity analyses were undertaken. The majority of company's results are deterministic (in line with what is presented in the report), The EAG scenarios are deterministic, but base-case is from both deterministic and probabilistic analysis.

**Table 32: Company's Base Case cost effectiveness analysis deterministic results for givinostat**

| Scenario | ECM | | Givinostat | | Incremental costs (£) | Incremental QALYs* | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| Company base-case | [redacted] | 19.3 | [redacted] | 6.1 | [redacted] | 22.4 | [redacted] | - |

**1.7x severity modifier applied to patient and carer incremental QALYs*

## 5.2 Company's sensitivity analyses

The company undertook sensitivity analyses in response to clarification questions and are presented in Table 33.

**Table 32 company's sensitivity analyses in response to clarification questions**

| Scenario | ECM | | Givinostat | | Incremental costs (£) | Incremental QALYs* | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| B8. Monitoring costs | £99,448 | 6.1 | [redacted] | 19.3 | [redacted] | 22.4 | [redacted] | +0.85% |
| B9. multiplier to estimate costs not captured by health states, tertiary care, etc.. | £286,991 | 6.1 | [redacted] | 19.3 | [redacted] | 22.4 | [redacted] | +2.5% |
| B.17 multiplier to estimate costs/utilities health states 8&7 | £107,876 | 6.1 | [redacted] | 19.1 | [redacted] | 22.5 | [redacted] | +0.9% |
| B. 23 discount rate 3.5% | Not Reported | | | | | | [redacted] | -18.9% |

**1.7x severity modifier applied to patient and carer incremental QALYs*

## 5.3 Model validation and face validity check

The company provided details of an external validation of the submitted model. In addition to this the EAG conducted the own face validity checks and calculation checks. The EAG did not identify or correct any relevant modelling errors.

Initial checks included checking that the model results match those in the report and company responses to clarification questions, re-running the model to replicate those results, checking that unseeded PSA runs produce similar results to the company's submitted PSA results, and checking the model structure, state transitions, and assumptions made in the model reflect the submission documents. The EAG also checked the key model formulae. This also included the black box tests described in Table 33.

**Table 33 Black box validation tests conducted by the EAG**

| Black box test | Expected result | Submitted model result |
|---|---|---|
| Checking if the ICER increases with higher drug prices? | Yes | Yes |
| Do the results change when the time horizon is extended/shortened | Yes | Yes |
| Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR? | Yes | Yes |
| Calculate the sum of the number of patients in each health state is equal to 100% | Health state occupancy should add up to 100% | Health state occupancy adds up to 100% |
| Are all probabilities between 0 and 1? | Yes | Yes |
| Are patients are dead at the end of the lifetime time horizon? | Yes | Yes |
| Set all utilities to 1 | The QALYs accumulated at a given time would be the same as the life-years accumulated at that time | The accumulated QALYs are equal to the accumulated life-years |
| Set all utilities to 0 | No utilities will be accumulated in the model | No utilities are accumulated in the model |

| | | |
|---|---|---|
| Set all input costs to 0 | No costs will be accumulated in the model at any time | No costs are accumulated in the model |
| Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal | Same life-years and QALYs should be accumulated for all treatment at any time | The same number of life-years and QALYs are accumulated |
| The above test with costs set to be equal between treatment arms | Incremental costs and QALYs should be zero | Incremental costs and QALYs are equal to zero |
| Are total life years greater than the total QALYs? | Yes | Yes |
| Are undiscounted results greater than discounted results? | Yes | Yes |
| Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected? | Yes | Yes |
| Set the discount rates to a higher value | Total discounted costs and QALYs should decrease | Total discounted costs and QALYs decrease |
| Is there a large difference between deterministic and probabilistic results? | Some difference is expected but it should not be large | Deterministic and probabilistic analyses produced similar results |
| Are costs higher after setting the inflation rate for previous years higher? | Yes | Yes |

The EAG intended to conduct more exhaustive white box testing where irregular results were identified in black box testing, however the company model passed all black box tests that the EAG conducted. The EAG did not find any errors with model formulas or VBA coding in investigations of the model.

# 6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

## 6.1 Exploratory and sensitivity analyses undertaken by the EAG

Exploratory and sensitivity analyses undertaken by the EAG are described in Table 34. These were conducted as both deterministic and probabilistic analyses, with 1000 samples being utilised for the latter.

**Table 34: Description of exploratory and sensitivity analyses undertaken by the EAG**

| Analysis | Section(s) of report | Details |
|---|---|---|
| Scenario 1. 3.5% discounting of both costs and effects | Section 4.2.5 and Key Issue 6 | The company applied a 1.5% discount rate to effects beyond 30 years with justification that givinostat confers a longer term benefit. The EAG notes that the NICE reference case is 3.5% discounting for both cost and QALYs. The EAG considers this inappropriate as both the ataluren and vamorolone appraisals utilised 3.5% discounting throughout the time horizon. EAG clinical experts also advised that the longer term benefit of givinostat, beyond discontinuation of treatment, is unknown. |
| Scenario 2. Alternative NHM calibration | Section 4.2.6 and Key Issue 9 | The company base case was calibrated to 50 year survival estimated by clinical experts (2.8%) and median age at loss of ambulation (12.1 years, as reported by UK real world data).<br><br>In this scenario the EAG explores calibration to the best available survival estimates at ages 10, 20, 30, and 40, and to UK real world data on median age starting ventilation (18.1 years) and starting full time ventilation (20.5 years). UK real-world data (in the stopped corticosteroid [GCS] group) were used at age 10 (100%), 20 (97%) and 30 (29.8%). This real-world data was |

| | | |
|---|---|---|
| | | limited to patients up to age 38 giving a potentially unrealistic estimate for age 40 survival (0.6%). Instead the clinical feedback estimate at age 40 (12.3%) was used. |
| Scenario 3. Include caregiver QALYs for ECM arm | Section 4.2.7 and Key Issue 7 | Clarification question B13<br><br>The EAG preferred accounting for carer quality of life on both ECM and Givinostat arms using the disutility decrements method. |
| Scenario 4. Change caregiver utility impact calculation | Section 4.2.7 and Key Issue 7 | The company's base case overestimates impact on caregiver quality of life, the EAG correct this by applying decrements accepted for decision making in TA1031 as detailed in Table 28, Section 4.2.7. |
| Scenario 5. Changing the number of caregivers | Section 4.2.7 and Key Issue 7 | This scenario changes the caregiver impact by varying the number of caregivers as in TA1031: 1 at ambulatory states and 2 at non-ambulatory states.[3] |
| Scenario 6. Utilities and costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") | Sections 4.2.7 and 4.2.8 and Key Issue 8 | The base case company submission assumes costs and utilities for states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") to be the same. The EAG considers that this does not account for cost and utility impacts of moving from only nighttime ventilation to needing full ventilation.<br><br>In this scenario the EAG uses utilities and costs from the BOI study, as reported in Table 27 and Table 31, respectively. |
| Scenario 7. Including givinostat monitoring costs | Section 4.2.8 | Clarification question B8<br><br>Monitoring costs as per company's scenario but with consultant led appointments as detailed in Table 30. |
| Scenario 8. Including costs due to tertiary care and | Section 4.2.8 | Clarification question B9. multiplier estimated from Landfeldt et al. 2014 |

| | | |
|---|---|---|
| medical aids not captured in HERCULES | | to estimate the health state costs inclusive of non-medical community services, aids, devices, and investments increases |
| Scenario 9. Lower severity modifier to account for uncertainty | Sections 4.2.7 | Limits the incremental QALYs to which the appropriate severity modifier (1.7x in company's base case) is applicable to patient QALYs, excluding caregiver QALYs, as detailed in section 4.2.7. |
| Scenario 10. MAIC hazard ratio on LOA applied to transition probabilities | Sections 3.4 and Section 4.2.6 and Key Issues 10 and 11 | Applies the MAIC hazard ratio for age at LOA, matched to the UK registry study, directly to the transition probability for late ambulatory to transfer. Bootstrap SE is used for uncertainty. Further details in main text. |
| Scenario 11. MAIC CINRG DHNS registry and acceleration factors | Sections 3.4 and Section 4.2.6 and Key Issue 4, 5, 10 and 11 | Uses Kaplan-Meier data for age at LOA in givinostat, weighted to an alternative registry source (CINRG DHNS), and applies acceleration factors derived from the alternative registry source to estimate age at NIV and age at FVC <1L. |
| Scenario 12. MAIC hazard ratio matched to CINRG DHNS on LOA applied to transition probabilities | Sections 3.4 and Section 4.2.6 and Key Issues 4, 5, 10 and 11 | Applies the MAIC hazard ratio for age at LOA, matched to the CINRG DHNS study, directly to the transition probability for late ambulatory to transfer. Bootstrap SE is used for uncertainty. |
| Scenario 13. MAIC hazard ratio matched to CINRG DHNS on LOA applied to all ambulation related transition probabilities | Sections 3.4 and Section 4.2.6 and Key Issues 4, 5, 10 and 11 | Applies the MAIC hazard ratio for age at LOA, matched to the CINRG DHNS study, directly to the transition probabilities for early ambulatory to late ambulatory, late ambulatory to transfer, and transfer to HTMF with no ventilation. Bootstrap SE is used for uncertainty. |

[redacted]In scenario 11 the EAG apply alternative acceleration factors derived from the CINRG DHNS (provided by the company in Table 7 of their clarification response) to digitized Kaplan-Meier data from weighted givinostat patients (EPIDYS/OLE) and ECM patients (CINRG DHNS) provided in Appendix Figure 3 of the company submission. Individual patient data were

estimated from digitized Kaplan-Meier data using the Guyot algorithm[67] for ECM (CINRG DHNS) for age at LOA, age at pFVC <50% and age at FVC <1L, and for givinostat (OLE/EPIDYS) for age at LOA. Note that Kaplan-Meier data for age at NIV was not available in CINRG DHNS, and so pFVC <50% was used as a proxy for this, following the company's approach in their clarification response.

Survival times were then multiplied by CINRG DHNS derived acceleration factors to estimate Kaplan-Meier data for age at NIV and age at FVC <1L in givinostat patients. Independent survival curves were fitted to all outcomes to estimate median time-to-event (given that data were not fully mature), with a log-normal distribution providing the best statistical and visual fit for all outcomes. These median time-to-event estimates were then used in the model to estimate hazard ratios using SOLVER, following the company's modelling approach. The hazard ratios were applied to transition probabilities from the company's base-case NHM.

In Scenario 10 and 12 the EAG apply hazard ratios from the MAIC directly to the NHM of the company submission. The company estimated hazard ratios for age at loss of ambulation, age at non-invasive ventilation, and age at FVC<1L.

The EAG agrees with the company that the alignment of these hazard ratios to transition probabilities is not exact. The EAG applies the assignment in Table 35 where double counting of treatment effects is minimised. This assumes that givinostat only has a treatment effect on LOA (i.e., transition from State 2 (Late ambulatory) ("Patient cannot stand from supine but can walk/run 10mt") to State 3 (Transfer) ("Patient no longer has the ability to walk or stand from supine but is able to stand assisted")) and that the impact on later health state occupancy (i.e., outcomes) is due only to delayed LOA. This aligns with the position stated by the company in Company Submission Section B.3.8 and B.3.3.4, and reiterated in response to clarification questions B3 and B4.

As a further sensitivity analysis, the EAG applies the preferred MAIC hazard ratios (i.e., those using the CINRG DHNS as described in Section 3.4) to all ambulatory transitions in Scenario 13. Details area gain included in Table 35. However, the EAG position is that applying the hazard ratio to these other transitions double counts treatment effects.

Unlike the company base case which used fixed estimates of the hazard ratios from SOLVER, this scenario propagates uncertainty in the MAIC HR on LOA by representing it as a Normal distribution on the log hazard ratio scale with standard deviations estimated from the 95% CI.

**Table 35: HRs applied to health state transitions in the CEM in company submission and in scenarios 10, 12 and 13 using the MAIC results**

| Health state transitions | HR in company submission | HR from MAICs for each affected scenario |
|---|---|---|
| State 1 (Early ambulatory) to state 2 (Late ambulatory)[a] | 0.51 | Scenarios 10 and 12: 1<br><br>Scenario 13. MAIC against CINRG DHNS:<br>0.451 (0.249, 0.832)<br>Modelled as log HR with Normal(mean = -0.7962879, standard deviation = 0.3077499) |
| State 2 (Late ambulatory) [a] to state 3 (Transfer)[b] | 0.51 | Scenario 10. MAIC against UK registry:<br>0.184 (0.127, 0.261)<br>Modelled as log HR with Normal(mean = -1.69282, standard deviation = 0.1837585)<br><br>Scenario 12. MAIC against CINRG DHNS:<br>0.451 (0.249, 0.832)<br>Modelled as log HR with Normal(mean = -0.7962879, standard deviation = 0.3077499)<br><br>Scenario 13. As in scenario 12. |
| State 3 (Transfer)[b] to state 4 (HTMF, no ventilation)[c] | 0.51 | Scenarios 10 and 12: 1<br><br>Scenario 13. MAIC against CINRG DHNS:<br>0.451 (0.249, 0.832)<br>Modelled as log HR with Normal(mean = -0.7962879, standard deviation = 0.3077499) |
| State 4 (HTMF, no ventilation)[c] to state 5 (No HTMF, no ventilation)[d] | 0.39 | 1 |
| State 5 (No HTMF, no ventilation)[d] to state 7a (No HTMF, night-time ventilation)[f] | 0.39 | 1 |
| State 7a (No HTMF, night-time ventilation)[f] to state 8a (Full time ventilation)[g] | 0.46 | 1 |
| State 4 (HTMF, no ventilation) to state 6 (HTMF, night-time ventilation)[d] | 0.39 | 1 |
| State 6 (HTMF, night-time ventilation)[e] to state 7b (No HTMF, night-time ventilation)[f] | 0.46 | 1 |
| State 7b (No HTMF, night-time ventilation)[f] to state 8b (Full time ventilation)[g] | 0.46 | 1 |

| Mortality transitions | HR in company submission | |
|---|---|---|
| From state 1 - Early ambulatory | 1.00 | 1.00 |
| From state 2 - Late ambulatory | 1.00 | 1.00 |
| From state 3 - Transfer | 1.00 | 1.00 |
| From state 4 - HTMF, no ventilation | 1.00 | 1.00 |
| From state 5 - No HTMF, no ventilation | 1.00 | 1.00 |
| From state 7a - No HTMF, night-time ventilation | 1.00 | 1.00 |
| From state 8a - Full time ventilation | 1.00 | 1.00 |
| From state 6 - HTMF, night-time ventilation | 1.00 | 1.00 |
| From state 7b - No HTMF, night-time ventilation | 1.00 | 1.00 |
| From state 8b - Full time ventilation | 1.00 | 1.00 |

Abbreviations: CEM, cost-effectiveness model; HR, hazard ratio; HTMF, hand-to-mouth function.

a. Patient cannot stand from supine but can walk/run 10mg
b. Patient no longer has the ability to walk or stand from supine but is able to stand assisted
c. Brooke <=4, FVC%>=50%
d. Brooke >4, FVC%>=50%
e. Brooke <=4, 30<=FVC%<50%
f. Brooke >4, 30<=FVC%<50%
g. FVC%<30%

## 6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The impact of the scenarios on costs, QALYs and ICER are presented in Table 37 for deterministic results. The 1.7x severity modifier remains unchanged from the company's base case and applied to patient and carer incremental QALYs. . We see that the greatest impact on the ICER is in from Scenario 12 (MAIC hazard ratio matched to CINRG DHNS on LOA applied to transition probabilities), scenario 5 (Changing the number of caregivers), scenario 4 (Change caregiver utility impact calculation) and scenario 9 (Lower severity modifier to account for uncertainty).

Scenario 1 (3.5% discounting of both costs and effects) has a moderate impact on the ICER. Other scenarios related to treatment effects (i.e., Scenarios 10, and 13) have a lower impact on the ICER than Scenario 12 (MAIC hazard ratio matched to CINRG DHNS on LOA applied to transition probabilities).

The results of additional calibration in Scenario 2 (Alternative NHM calibration) are presented in Table 36. The EAG notes that fit to DMD clinical endpoints (i.e., median age loss of ambulation, starting ventilation, and starting full time ventilation) and survival are poor. The EAG views that the model is likely too inflexible to improve fit to available data.

**Table 36: Calibration of the Natural History Model using the Solver functionality in MS Excel for Scenario 2 "Alternative NHM calibration"**

| | Company's Calibration | | | | EAG Calibration | | | |
|---|---|---|---|---|---|---|---|---|
| | Results | Target | applied? | Delta | Results | Target | applied? | Delta |
| **Median age at: (in years)** | | | | | | | | |
| Loss of ambulation | 12.1 | 12.12 | Yes | -0.29% | 12.7 | 12.12 | Yes | 4.52% |
| Starting ventilation | 16.0 | 18.05 | Yes | -11.36% | 16.6 | 18.05 | Yes | -8.13% |
| Starting full time ventilation | 20.3 | 20.49 | Yes | -0.76% | 19.5 | 20.49 | Yes | -4.83% |
| Death | 25.5 | 28.01 | No | -8.97% | 26.5 | 28.01 | No | -5.41% |
| **Proportion surviving at (years)** | | | | | | | | |
| 10 | 99.4% | 100.0% | Yes | -0.56% | 99.7% | 100.00% | Yes | -0.25% |
| 20 | 74.8% | 88.2% | Yes | -15.20% | 75.3% | 97.03% | Yes | -22.35% |
| 30 | 32.7% | 45.0% | No | -27.29% | 38.8% | 29.79% | Yes | 30.32% |
| 40 | 10.4% | 12.3% | No | -14.88% | 17.2% | 12.25% | Yes | 40.33% |
| 50 | 2.8% | 2.8% | Yes | 1.82% | 7.2% | 2.75% | Yes | 160.45% |

**Table 37: Results of the EAG's scenario and exploratory analysis (deterministic results)**

| Scenario | ECM | | Givinostat | | Incremental costs (£) | Incremental QALYs* | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| Company base-case | £99,448 | 6.14 | [redacted] | 19.33 | [redacted] | 22.41 | [redacted] | - |
| Scenario 1 | £99,448 | 6.08 | [redacted] | 16.42 | [redacted] | 17.57 | [redacted] | 27.54% |
| Scenario 2 | £103,481 | 6.43 | [redacted] | 18.52 | [redacted] | 20.55 | [redacted] | 7.66% |
| Scenario 3 | £99,448 | 6.14 | [redacted] | -33.79 | [redacted] | 22.41 | [redacted] | 0.00% |
| Scenario 4 | £99,448 | 6.57 | [redacted] | 11.88 | [redacted] | 9.03 | [redacted] | 148.27% |
| Scenario 5 | £99,448 | 6.14 | [redacted] | 10.62 | [redacted] | 7.62 | [redacted] | 194.11% |
| Scenario 6 | £106,699 | 7.50 | [redacted] | 21.01 | [redacted] | 22.97 | [redacted] | -2.43% |
| Scenario 7 | £99,448 | 6.14 | [redacted] | 19.33 | [redacted] | 22.41 | [redacted] | 1.06% |
| Scenario 8 | £286,991 | 6.14 | [redacted] | 19.33 | [redacted] | 22.41 | [redacted] | 2.48% |
| Scenario 9 | £99,448 | 6.14 | [redacted] | 19.33 | [redacted] | 15.98 | [redacted] | 40.20% |
| Scenario 10 | £99,448 | 6.14 | [redacted] | 16.32 | [redacted] | 17.30 | [redacted] | 20.19% |
| Scenario 11 | £99,448 | 6.14 | [redacted] | 17.45 | [redacted] | 19.22 | [redacted] | 12.30% |
| Scenario 12 | £99,448 | 6.14 | [redacted] | 9.19 | [redacted] | 5.19 | [redacted] | 262.33% |
| Scenario 13 | £99,448 | 6.14 | [redacted] | 16.23 | [redacted] | 17.15 | [redacted] | 21.11% |

**1.7x severity modifier applied to patient and carer incremental QALYs.*

## 6.3 EAG's preferred assumptions

The incremental impact of the scenarios on EAG base case costs, QALYs and ICER in Table 39 for deterministic results and Table 40 for probabilistic results. The severity modifier is applied to patient and carer incremental QALYs as in the company's base case but drops from 1.7x to 1.2x in relation to the change in the absolute shortfall in QALYs.. In line with the NICE reference case and assumptions in the ataluren and vamorolone appraisals, discounting at 3.5% is applied to both costs and effects over the full time horizon. The company base case applied 1.5% discounting to effects beyond 30 years.

The EAG notes that the updated NHM underestimates survival compared to clinical opinion at ages 15, 20, 25, 30, and 35, only matching at 40 and 50 years (Table 24). The EAG also notes that it consistently underestimates the age for DMD patients of starting ventilation, starting full time ventilation and death compared to UK real world data (Table 25). The EAG considers that this could overestimate the benefit of givinostat as the natural history (and thus potential for benefit) is greater. However, given the poor calibration of the NHM to these additional data (Scenario 2 in Section 6.2 with results in Table 36) this scenario is not included in the EAGs preferred base case. The EAG views that the model is likely too inflexible to improve fit this available data.

Caregiver QALYs are included on both the givinostat and ECM arm. The company included caregiver QALYs only on the givinostat arm. The EAG argues this does not give a fair exploration of the impact of caregiver QALYs on givinostat as the incremental caregiver QALYs are not estimated.

The Company use a vignette study to calculate utility decrements relative to the general population in full health and include a bereavement disutility after death. The EAG prefers utility decrements relative to early ambulatory health state from the BOI study, these were preferred in TA1031, the appraisal for vamorolone and removed the post-death bereavement disutility.

The EAG furthermore prefers to adjust the number of caregivers to reflect the increased caregiver burden of the non-ambulatory health states (4-8) compared to the ambulatory health states (1-3). This matches those assumed in the vamorolone NICE appraisal.[3]

The EAG prefers to use cost and utility sources that account for the impacts of moving from only night time ventilation to needing full ventilation, while no impact was assumed in the company base case. In response to clarification question B17 the company provided justification that this was due to limited data, and due to the HERCULES model, which provided state costs, not separating the extent of ventilation. The EAG prefers costs and utilities to come from the BOI study in its base case. This was informed by a Delphi panel measured quality of life for patients and caregivers in the UK using EQ-5D as part of Project HERCULES and state definitions align with those of the company model, including separate estimates for states 7 and 8.

The EAG received clinical advice that treatment would be administered in tertiary care but monitoring through secondary care. In clarification question B8, the company acknowledged the SPC for givinostat recommends regular monitoring of platelet counts and triglycerides for the purposes of adjusting the dosage. However, the company assumed non-consultants led monitoring but the EAG prefers to assume that a specialist consultant is required.

The EAG prefers to account for costs of tertiary care and medical aids not captured in HERCULES this was done by recalculating the multiplier estimated by the company and to exclude costs not applicable relevant to decision making in the UK and applying the multiplier to BOI medial costs as detailed in Table 31 of section 4.2.8.

As explained in Section 3.5.3 the EAG prefers to use a hazard ratio for LOA estimated by an MAIC against the CINRG DHNS registry instead of against the UK registry. In brief, this was due to proportions on deflazacort likely being higher in CINHRG and closer to EPIDYS than in the UK registry, additional reporting by CINRG DHNS of important prognostic variables for matching, and that CINRG DHSNS is a global registry better aligned with the multi-centre international nature of EPIDYS. While the UK registry may better reflect the UK population of interest, the EAG argues that this makes it appropriate for natural history modelling, rather than for estimation of relative treatment effects.

The EAG further prefers to apply the MAIC LOA hazard ratio only to the transition from State 2 (Late ambulatory) ("Patient cannot stand from supine but can walk/run 10mt") to State 3 (Transfer) ("Patient no longer has the ability to walk or stand from supine but is able to stand assisted")). The EAG argues that the hazard ratios to transitions between states 1 (Early ambulatory) and 2 (Late ambulator) or between states 3 (Transfer) and 4 (HTMF, no ventilation) would double count treatment effects. The impact on later health state occupancy (i.e., outcomes) is due only to delayed LOA. This aligns with the position stated by the company in Company Submission Section B.3.8 and B.3.3.4, and reiterated in response to clarification questions B3 and B4.

**Table 38: Scenarios included in EAG Preferred assumptions**

| Scenario used as EAG preferred assumption |
|---|
| Scenario 1. 3.5% discounting of both costs and effects |
| Scenario 3. Include caregiver QALYs for ECM arm |
| Scenario 4. Change caregiver utility impact calculation |
| Scenario 5. Changing the number of caregivers |
| Scenario 6. Utilities and costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") |
| Scenario 7. Including givinostat monitoring costs |
| Scenario 8. Including costs due to tertiary care and medical aids not captured in HERCULES |

| Scenario 12. MAIC hazard ratio matched to CINRG DHNS on LOA applied to transition probabilities |
|---|

**Table 39: EAG preferred assumptions added incrementally and EAG base-case (deterministic results)**

| Interventions | Total Costs | Total Patient QALYs | Total QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs*ǂ (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|
| Company's base-case | | | | | | | |
| ECM | £99,448 | 6.14 | 6.14 | | | | |
| Givinostat | [redacted] | 10.15 | 19.33 | [redacted] | 4.00 | 22.41* | [redacted] |
| Company's base-case + EAG's preferred assumption S1: 3.5% discounting of both costs and effects | | | | | | | |
| ECM | £99,448 | 6.08 | 6.08 | | | | |
| Givinostat | [redacted] | 9.57 | 16.42 | [redacted] | 3.48 | 17.57* | [redacted] |
| Company's base-case + S1 + EAG's preferred assumption S3: Include caregiver QALYs for ECM arm | | | | | | | |
| ECM | £99,448 | 6.08 | -26.09 | | | | |
| Givinostat | [redacted] | 9.57 | -15.76 | [redacted] | 3.48 | 15.57* | [redacted] |
| Company's base-case + S1 + S3 + EAG's preferred assumption S4: Change caregiver utility impact calculation | | | | | | | |
| ECM | £99,448 | 6.08 | 6.61 | | | | |
| Givinostat | [redacted] | 9.57 | 10.89 | [redacted] | 3.48 | 7.29* | [redacted] |
| Company's base-case + S1 + S3 + S4 +EAG's preferred assumption S5: Changing the number of caregivers | | | | | | | |
| ECM | £99,448 | 6.08 | 6.92 | | | | |

| Interventions | Total Costs | Total Patient QALYs | Total QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs*‡ (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|
| Givinostat | [redacted] | 9.57 | 11.40 | [redacted] | 3.48 | 7.62* | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 +EAG's preferred assumption S6: Utilities and costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") | | | | | | | |
| ECM | £106,699 | 7.36 | 8.20 | | | | |
| Givinostat | [redacted] | 10.62 | 12.46 | [redacted] | 3.26 | 5.11‡ | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 + S6 + EAG's preferred assumption S7: Givinostat monitoring costs | | | | | | | |
| ECM | £106,699 | 7.36 | 8.20 | | | | |
| Givinostat | [redacted] | 10.62 | 12.46 | [redacted] | 3.26 | 5.11‡ | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 + S6 +S7 + EAG's preferred assumption S8: Including costs due to tertiary care and medical aids not captured in HERCULES | | | | | | | |
| ECM | £162,904 | 7.36 | 8.20 | | | | |
| Givinostat | [redacted] | 10.62 | 12.46 | [redacted] | 3.26 | 5.11‡ | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 + S6 +S7 + S8 + EAG's preferred assumption S12: MAIC hazard ratio matched to CINRG DHNS on LOA applied to transition probabilities | | | | | | | |
| ECM | £162,904 | 7.36 | 8.20 | | | | |
| Givinostat | [redacted] | 7.94 | 8.43 | [redacted] | 0.58 | 0.27‡ | [redacted] |

**1.7x severity modifier applied to patient and carer incremental QALYs.*

*‡1.2x severity modifier applied to patient and carer incremental QALYs.*

**Table 40: EAG base-case probabilistic results after 1000 iterations run**

| Interventions | Total Costs | Total Patient QALYs | Total QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs*‡ (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|
| Company's base-case | | | | | | | |
| ECM | £99,201 | 6.13 | 6.13 | | | | |
| Givinostat | [redacted] | 10.12 | 19.32 | [redacted] | 4.00 | 22.43* | [redacted] |
| Company's base-case + EAG's preferred assumption S1 : 3.5% discounting of both costs and effects | | | | | | | |
| ECM | £98,932 | 6.09 | 6.09 | | | | |
| Givinostat | [redacted] | 9.57 | 16.45 | [redacted] | 3.49 | 16.96* | [redacted] |
| Company's base-case + S1 + EAG's preferred assumption S3: Include caregiver QALYs for ECM arm | | | | | | | |
| ECM | £99,285 | 6.12 | -26.05 | | | | |
| Givinostat | [redacted] | 9.62 | -15.69 | [redacted] | 3.50 | 16.80* | [redacted] |
| Company's base-case + S1 + S3 + EAG's preferred assumption S4: Change caregiver utility impact calculation | | | | | | | |
| ECM | £98,805 | 6.07 | 6.59 | - | | | |
| Givinostat | [redacted] | 9.54 | 10.88 | [redacted] | 3.47 | 7.02* | [redacted] |
| Company's base-case + S1 + S3 + S4 +EAG's preferred assumption S5: Changing the number of caregivers | | | | | | | |

| Interventions | Total Costs | Total Patient QALYs | Total QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs*ǂ (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|
| ECM | £99,296 | 6.11 | 6.93 | - | | | |
| Givinostat | [redacted] | 9.60 | 11.42 | [redacted] | 3.49 | 7.30* | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 +EAG's preferred assumption S6: Utilities and costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") | | | | | | | |
| ECM | £106,699 | 7.36 | 8.20 | | | | |
| Givinostat | [redacted] | 10.62 | 12.47 | [redacted] | 3.26 | 5.13ǂ | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 + S6 + EAG's preferred assumption S7: Givinostat monitoring costs | | | | | | | |
| ECM | £106,699 | 7.37 | 8.19 | | | | |
| Givinostat | [redacted] | 10.63 | 12.44 | [redacted] | 3.26 | 5.11ǂ | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 + S6 +S7 + EAG's preferred assumption S8: Including costs due to tertiary care and medical aids not captured in HERCULES | | | | | | | |
| ECM | £162,904 | 7.37 | 8.20 | | | | |
| Givinostat | [redacted] | 10.62 | 12.45 | [redacted] | 3.26 | 5.12ǂ | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 + S6 +S7 + S8 + EAG's preferred assumption S12: MAIC hazard ratio matched to CINRG DHNS on LOA applied to transition probabilities | | | | | | | |
| ECM | £162,904 | 7.36 | 8.18 | | | | |
| Givinostat | [redacted] | 7.96 | 8.42 | [redacted] | 0.61 | 0.29ǂ | [redacted] |

| Interventions | Total Costs | Total Patient QALYs | Total QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs*‡ (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|

**1.7x severity modifier applied to patient and carer incremental QALYs.*

*‡1.2x severity modifier applied to patient and carer incremental QALYs.*

## 6.4 Conclusions of the cost effectiveness section

The EAG did not identify or correct any relevant modelling errors (Section 5.3).

The EAG considers that the submitted model is largely aligned with the decided scope, although the use of 1.5% discounting of effects beyond 30 years means the analysis differs from the NICE reference case. The EAG does not accept this discounting and 3.5% was followed in the recent ataluren and vamorolone NICE appraisals and in published models. There is also no evidence available on long-term benefit of givinostat beyond discontinuation and EAG clinical advice was that this long-term benefit is unknown.

The EAG advises that the company base case does not provide a complete and unbiased estimate of the ICER. The omissions are the exclusion of caregiver QALYs for the ECM arm, lack of distinction between utilities and costs of states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation"), omission of givinostat monitoring costs and omission of tertiary care and medical aids costs not captured by HERCULES. Company analyses which the EAG recommend changing are the caregiver utility impact, number of caregivers needed by patients, and the modelling of treatment effect of givinostat. The latter has the greatest impact on the ICER. In the company submission SOLVER was used to calibrate the economic model to a givinostat LOA curve matched to UK registry data. The EAG prefers to directly use an estimated hazard ratio from a MAIC matched to, in the EAG's view, the more appropriate CINRG DHNS registry. The EAG also prefers to apply this hazard ratio only to the transition from state 2 (Late ambulatory) to states 3 (transfer) to avoid doublet counting treatment effects. These omissions and analyses have been addressed in the EAG preferred case.

The EAG notes that the updated NHM underestimates survival compared to clinical opinion at ages 15, 20, 25, 30, and 35, only matching at 40 and 50 years (Table 24). The EAG also notes that it consistently underestimates the age for DMD patients of starting ventilation, starting full time ventilation and death compared to UK real world data (Table 25). The EAG considers that this could overestimate the benefit of givinostat as the natural history (and thus potential for benefit) is greater. The EAG explored calibration to the best available survival estimates at ages 10, 20, 30, and 40, and also to UK real world data on median age starting ventilation (18.1 years) and starting full time ventilation (20.5 years). UK real-world data (in the stopped corticosteroid [GCS] group) were used at age 10 (100%), 20 (97%) and 30 (29.8%). This real-world data was limited to patients up to age 38 giving a potentially unrealistic estimate for age 40 survival (0.6%). Instead the clinical feedback estimate at age 40 (12.3%) was used. However, the EAG noted that calibration did not result in a close match to the observed data and chose not to use this modification to the NHM in its preferred assumptions (Table 36). The EAG views that the model is likely too inflexible to improve fit to available data and this remains a source of bias in the ICERs of both the company and EAG analyses.

The EAG notes that the HERCULES model structure transition probabilities cannot be directly informed by the primary outcome of EPIDYS (i.e., mean change in the time taken to complete a standard four-stair climb between baseline and 18 months). This leads to the model relying on non-randomised evidence to inform treatment effects, via an uITC, which the EAG has rated as being at critical risk of bias. The EAG suggests an alternative model structure using continuous outcomes as a health state. However, the EAG also notes disadvantages to this approach, including the difficulty in estimating costs and utilities, and in matching to an external control if the control arm of EPIDYS is not viewed to be representative of clinical practice. The EAG considers changing the model structure to have an unknown impact on the cost-effectiveness results so the potentially inappropriate structure and reliance on uITC remain a source of bias.

The difference in ICER between the company base case and EAG preferred assumptions is primarily driven by the use of an MAIC hazard ratio matched to CINRG DHNS on LOA applied to transition probabilities (Scenario 12, Key Issues 4, 5, 10 and 11), changing the number of caregivers (scenario 5, Key Issue 7), changing the caregiver utility calculation (scenario 4, key issue 7), and applying 3.5% discounting over the full time horizon (scenario 1, Key Issue 6). Other changes have less of an impact on the ICER, including the use of utilities and costs that distinguish between states 8 and 7 (scenario 6, Key Issue 8), and changes to cost calculations (scenarios 7 and 8). As noted, it was not feasible to account for Key Issue 10 (Mismatch of HERCULES NHM and available RCT data on givinostat) in a scenario and the scenario related to Key Issue 9 (Overestimation by NHM of survival and DMD clinical progression events) did not lead to improved model fit.

# 7 Severity and Innovation

In the company's base case expected QALYs for sick patients (ECM arm) are 6.14, while the expected QALYs in the general population are 32.5, resulting in an absolute QALY short fall of 29.1 and corresponding to a severity modifier of 1.7x. The probabilistic discounted incremental QALY gain for givinostat is 13.20, this corresponds to a severity weighted Incremental QALY gain of 22.43 and probabilistic ICER of [redacted] for the company's base case. The severity modifier was applied to the Incremental carer QALYs gain of 9.19.

In the EAG's base case expected QALYs for sick patients (ECM arm) are 7.36, while the expected QALYs in the general population are 24.60, resulting in an absolute QALY short fall of 17.2 and corresponding to a severity modifier of 1.2x. The probabilistic discounted incremental QALY gain for givinostat is 0.61, this corresponds to a severity weighted Incremental QALY gain of 0.360 and probabilistic ICER of [redacted] for the EAG base case. Note while the incremental carer QALYs loss of -0.37 was included in this calculation, the severity modifier was not applied to it as discussed in section 4.2.7 and the method detailed in Table 29. The total incremental QALYs with severity modifier applied to the incremental patient QALYs alone or to both incremental patient and carer QALYs are presented for the EAG's incremental preferred assumptions in Table 42.

**Table 41 Total Incremental QALYs with and without severity modifiers for the EAG's incremental preferred assumptions (probabilistic results)**

| EAG Incremental Base Case | Incremental QALYs | | Total Incremental QALYs | | |
|---|---|---|---|---|---|
| | Patient | Carer | Without severity modifier applied | With severity modifier applied to patient incremental QALYs | With severity modifier applied to patient & carer incremental QALYs |
| Scenario 0 Company Base Case | 4.00 | 9.19 | 13.20 | 16.00 | 22.43 |
| Scenario 0 + 1 | 3.49 | 6.87 | 10.36 | 12.58 | 16.96 |
| Scenario 0 + 1 + 3 | 3.50 | 6.86 | 10.36 | 12.53 | 16.80 |
| Scenario 0 + 1 + 3 + 4 | 3.47 | 0.81 | 4.28 | 6.50 | 7.02 |
| Scenario 0 + 1 + 3 + 4 + 5 | 3.49 | 1.00 | 4.49 | 6.68 | 7.30 |
| Scenario 0 + 1 + 3 + 4 + 5 + 6 | 3.26 | 1.01 | 4.26 | 4.92 | 5.13 |
| Scenario 0 + 1 + 3 + 4 + 5 + 6 + 7 | 3.26 | 0.99 | 4.25 | 4.91 | 5.11 |
| Scenario 0 + 1 + 3 + 4 + 5 + 6 + 7 + 8 | 3.26 | 1.00 | 4.25 | 4.92 | 5.12 |
| EAG base case (Scenario 0 + 1 + 3 + 4 + 5 + 6 + 7 + 8 + 12) | 0.61 | -0.37 | 0.24 | 0.36 | 0.29 |

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# 9 APPENDICES

## 9.1 Appendix 1: Clinical Effectiveness ROBIS assessment

This appraisal of the systematic review of clinical effect was conducted with an amended version of ROBIS tool[15] to remove the synthesis domain as this is not relevant to the submission. The EAG's ROBIS assessment was conducted by one reviewer and checked by a second. Any disagreements were resolved by discussion.

| **DOMAIN 1: STUDY ELIGIBILITY CRITERIA** | |
|---|---|
| • Did the review adhere to pre-defined objectives and eligibility criteria? | Y |
| • Were the eligibility criteria appropriate for the scope? | PY |
| • Were eligibility criteria unambiguous? | PY |
| • Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | Y |
| • Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | PY |
| **Risk of bias judgement:** | LOW |

**Rationale:**

- The protocol was provided in response to clarification questions. The EAG asked the Company to report any post-protocol amendments to the review. The Company highlighted the following change which the EAG accept: '*In the NICE final scope inclusion and exclusion eligibility criteria (Table 8 in the original protocol and Table 9 in the update protocol) we listed a comparator as 'established clinical management without givinostat from multinational or UK natural history studies' in the original SLR protocol and 'established clinical management without givinostat from UK natural history studies' in the update SLR protocol. This should have been included in the 'intervention' row, and the 'comparators' should have been 'any'. The Company screened as if it was an 'intervention' and therefore amended the table during write up to reflect the criteria used during screening'*(C1).[16]
- The EAG highlight that the Company's searches included Ataluren (the comparator specified by NICE). In discussion with clinical advisors, the EAG accept the Company's argument that Ataluren is not a relevant comparator, so agree it does not need to form part of the review's findings. We note, however, that the Company have the studies and data for this intervention if required by the Committee.
- Studies published in languages other than English were excluded.

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES** | |
|---|---|
| 1. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | Y |
| 2. Were methods additional to database searching used to identify relevant reports? | Y |
| 3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | Y |
| 4. Were restrictions based on date, publication format, or language appropriate? | Y |
| 5. Were efforts made to minimize error in selection of studies? | Y |
| **Risk of bias judgement:** | **LOW** |

**Rationale:**

Searches were appropriately conducted and study selection clearly explained. Searches were limited to English language but, whilst the EAG would have preferred that language restriction be applied at study selection, the EAG are comfortable that no studies or reports have been omitted.

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL** | |
|---|---|
| 1. Were efforts made to minimize error in data collection? | Y |
| 2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | Y |
| 3. Were all relevant study results collected for use in the synthesis? | PY |
| 4. Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | PY |
| 5. Were efforts made to minimise error in risk of bias assessment? | Y |
| **Risk of bias judgement:** | **LOW** |
| **Rationale:** The EAG sought clarification on the conduct in checking data extraction and requested the company to repeat quality appraisal using the ROB 2 tool (C5 and C6).[16] The company completed the risk of bias assessment for two outcomes. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

## 9.2 Appendix 2: Overview of studies, data sources and outcomes

Listed as informing clinical effectiveness and included in the economic model in CS (mapped to NICE scope)

| NICE scope category | Key outcomes listed in CS | Outcome | Treatment comparison made in study | Source of data | CS states included company model | Recommended by EMA |
|---|---|---|---|---|---|---|
| **Walking ability (ambulation)** | **Four-stair climb (4SC)** | **Primary** | **Direct, randomised (vs. placebo)** | **EPIDYS Company Submission (Table 13)** | **Yes** | **Yes** |
| | Six-minute walking distance (6MWD) | Secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 13) | No | Yes |
| | Ten-metre walking test (10MWT) | Secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 13) | No | Yes |
| | Time-to-rise from floor (TTRF) | Secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 13) | No | Yes |
| | North Star Ambulatory Assessment (NSAA) | Key secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 13) | No | Yes |
| | | Key Secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | |
| | **Loss of ambulation** | **Secondary** | **Direct, randomised (vs. placebo)** | **EPIDYS Company Submission (Table 12)** | **Yes** | **Yes** |
| | **Age at loss of ambulation** | **Not specified** | **Direct, randomised (vs. placebo)** | **EPIDYS Company Submission (Table 12)** | **Yes** | **Yes** |
| | | **Secondary** | **Single arm (no comparator)** | **OLE Company Submission (Table 14)** | **Yes** | |
| | | **NA** | **Single arm (ECM)** | **UK registry study** | **Yes** | |
| Muscle function | Motor Function Measure Scale (MFM) | Key Secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | Yes |
| Muscle strength | Muscle strength evaluated by knee extension | Key secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 12) | No | Yes |
| | | Key secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | |
| | | Key secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 12) | No | Yes |

| NICE scope category | Key outcomes listed in CS | Outcome | Treatment comparison made in study | Source of data | CS states included company model | Recommended by EMA |
|---|---|---|---|---|---|---|
| | Muscle strength evaluated by elbow flexion measured by HHM | Key secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | |
| Ability to undertake activities of daily living | Egen Klassifikation (EK) scale (for non-ambulant patients) | Key Secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | Yes |
| | Barthel index (for non-ambulant patients) | Key Secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | Yes |
| Bone function | None reported | NA | NA | NA | No | No |
| Cardiac function | Cardiac function (ECG and echocardiogram) | Key Secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 12) | No | Yes |
| Concordance and optimisation of treatment | Evaluation of acceptability/palatability of the oral suspension | Key Secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 12) | No | No |
| Endocrine function | Weight, height, and BMI | Key Secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 12) – only collected at baseline | No | Yes |
| **Lung function** | **Respiratory function (FEV1 (L), FVC (L), FEV1/FVC (%) and PEF (L/min))** | **Key Secondary** | **Direct, randomised (vs. placebo)** | **EPIDYS Company Submission (Table 11)** | **Yes** | **Yes** |
| | | **Primary** | **Single arm (no comparator)** | **OLE Company Submission (Table 14)** | **No** | |
| | **Age at non-invasive ventilation** | **Key Secondary** | **Single arm (no comparator)** | **OLE Company Submission (Table 14)** | **Yes** | **Yes** |
| | | **Primary** | **Single arm (ECM)** | **UK registry study** | **Yes** | |
| | **Age at FVC<1L** | **Key Secondary** | **Single arm (no comparator)** | **OLE Company Submission (Table 14)** | **Yes** | **Yes** |
| | | **Secondary** | **Single arm (ECM)** | **UK registry study** | **Yes** | |
| | **Age at FVC<30%** | **Key Secondary** | **Single arm (no comparator)** | **OLE Company Submission (Table 14)** | **Yes** | **Yes** |
| | | **Secondary** | **Single arm (ECM)** | **UK registry study** | **Yes** | |
| Time in wheelchair | None reported | NA | NA | NA | No | Yes, (time to wheelchair) |

| NICE scope category | Key outcomes listed in CS | Outcome | Treatment comparison made in study | Source of data | CS states included company model | Recommended by EMA |
|---|---|---|---|---|---|---|
| Number of falls | None reported | NA | NA | NA | No | No |
| Time to scoliosis | Age at scoliosis surgery | Key Secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | Yes |
| Lower body function) | None reported | NA | NA | NA | No | Yes |
| Upper body function | Loss of upper limb function (PUL) | Key Secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | Yes |
| Mortality | Age at death | Key Secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | Yes |
| **Adverse effects of treatment** | **AEs and SAEs** | **Key secondary** | **Direct, randomised (vs. placebo)** | **EPIDYS (Table 12)** | **Yes** | **Yes** |
| | | **Primary** | **Single arm (no comparator)** | **OLE Company Submission (Table 14)** | **Yes** | **Yes** |
| Health related quality of life | PODCI | Key secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 12) | No | Yes |
| | PedsQL (paediatric patients) and SF-36 (adult patients) | Key Secondary | Single arm (no comparator) | OLE Company Submission (Table 14) | No | Yes |
| Others (not specified in NICE scope) | Mean change in VL MFF | Key secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 12) | No | No |
| | Cognitive function (Raven-coloured progressive matrices) | Key Secondary | Direct, randomised (vs. placebo) | EPIDYS Company Submission (Table 12) | No | Yes (cognitive tests suggested as exploratory outcomes, no specific test recommended) |

Text in bold are the outcomes listed in the CS as being included in the economic model.

Outcomes, data sources and inclusion in the company economic model are reproduced from the CS (details in 'source of data' column). Also listed is whether the EAG found a similar outcome included in the EMA guidance for clinical studies in DMD and the EAG's judgement on which outcome the company's outcome maps onto in the NICE scope.

## 9.3 Appendix 3: Risk of Bias assessment for EPIDYS key outcomes

Assessment conducted by the EAG using RoB 2 tool

| Domain | Signalling question | Four stair climb | Age at loss of ambulation | Loss of ambulation | Adverse effects (AEs) of treatment | Lung function | Comments |
|---|---|---|---|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Y | Y | Y | Y | Random assignment (using 2:1) ratio. Allocation according to a randomisation list generated by a statistician from the interactive response technology provider, accessed by site staff by phoning the provider's system to receive a packaging number |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | Y | Y | Y | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | N | N | N | N | Baseline differences between intervention groups did not suggest a problem with the randomisation process |
| | **Risk of bias judgement** | **Low** | **Low** | **Low** | **Low** | **Low** | **No concerns regarding the randomisation process** |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | N | N | N | N | Double-blind trial: "boys, investigators, and site and sponsor staff were masked to treatment assignment with the placebo suspension indistinguishable in appearance and taste to givinostat" |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | N | N | N | N | |
| | 2.3. If Y/PY/NI to 2.1/2.2: Were there deviations from the intended interventions that arose because of the trial context? | PN | PN | PN | PN | PN | No deviations from intended interventions that arose due to trial context are reported |
| | 2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | NA | NA | NA | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | NA | NA | NA | NA | |

| Domain | Signalling question | Four stair climb | Age at loss of ambulation | Loss of ambulation | Adverse effects (AEs) of treatment | Lung function | Comments |
|---|---|---|---|---|---|---|---|
| | 2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | NI | PY | PY | NI | Four-stair climb analyses were conducted in the Group A population in the CS, rather than the overall ITT population. Supportive post-hoc analyses in the overall ITT population were reported to be consistent with Group A. Although this was pre-planned for the trial, for the CS, the EAG would have preferred to see the analyses and data for Group A, Group B, and the overall population. This is because it is the overall population that informs the economic model. The EAG asked for this in clarification question A4 and A8 but the company did not provide this in full.<br><br>No details were presented regarding age at loss of ambulation (not a pre-specified outcome) or lung function (pre-specified outcome).<br><br>For loss of ambulation (pre-specified outcome) descriptive results for this outcome are presented in the adverse event section of the CS and in the main journal publication and likely appropriate.<br><br>AEs of treatment effect were analysed in the safety population which comprised those who had received >1 treatment dose (i.e. per protocol analysis). The EAG has no concerns with this because the safety population ended up including all patients, as all received >1 treatment dose. |
| | 2.7. If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised? | NA | NI | NA | NA | NI | No information reported for age at loss of ambulation and lung function in the CS. |
| | **Risk of bias judgement** | **Low** | **High** | **Low** | **Low** | **High** | **High risk for age at loss of ambulation and lung function because there is no information reported about these outcomes in the CS. No concerns for other outcomes.** |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | NI | PY | PY | NI | No patients highlighted as lost to follow-up in the overall population or the safety population. No information reported for age at loss of ambulation (not a pre-specified outcome in trial protocol) and lung function in the clinical effectiveness part of the CS. |

| Domain | Signalling question | Four stair climb | Age at loss of ambulation | Loss of ambulation | Adverse effects (AEs) of treatment | Lung function | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | N | NA | NA | N | No information reported for age at loss of ambulation and lung function in the clinical effectiveness part of the CS. |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | NI | NA | NA | NI | |
| | 3.4. If Y/PY/Ni to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | NI | NA | NA | NI | |
| | **Risk of bias judgement** | **Low** | **High** | **Low** | **Low** | **High** | **High risk for age at loss of ambulation and lung function because there is no information reported about these outcomes in the CS. No concerns for other outcomes.** |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | N | NI | N | N | N | No information on measurement of age at loss of ambulation (not pre-specified in protocol). Appropriate measurement other outcomes, as specified in EPIDYS trial protocol. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | PN | NI | PN | PN | PN | No information on measurement of age at loss of ambulation (not pre-specified in protocol). Unlikely that measurement would have differed between groups for other outcomes, which were pre-specified in protocol. |
| | 4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants? | N | NI | N | N | N | The protocol notes that “personnel involved in the study (Investigators, nurses, all other site personnel, clinical research associate (CRA), MedicalMonitors, Project Managers, and personnel involved in data management) will remain blind at all times”. All functional/ strength assessments were assessed by independent physiotherapists who were different to site personnel. No information for age at loss of ambulation. |
| | 4.4. If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | NA | NA | NA | NA | NA |
| | 4.5.: If Y/PY/NI to 4.4: Is it likely that assessment of the outcome | NA | NA | NA | NA | NA | |

| Domain | Signalling question | Four stair climb | Age at loss of ambulation | Loss of ambulation | Adverse effects (AEs) of treatment | Lung function | Comments |
|---|---|---|---|---|---|---|---|
| | was influenced by knowledge of the intervention received? | | | | | | |
| | **Risk of bias judgement** | **Low** | **Some concerns** | **Low** | **Low** | **Low** | **No information on measurement of age at loss of ambulation (not pre-specified in protocol). No concerns for other outcomes.** |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | Y | NI | PY | Y | NI | Protocol dated Apr 2020 and finalised before study unblinding. Age at loss of ambulation not a pre-specified outcome. Lung function was a pre-specified outcome in the protocol but there is no information about it in the clinical effectiveness section of the CS or journal article about analysis for these outcomes, therefore no assessment was possible. Loss of ambulation pre-specified outcome and descriptive results reported in main journal publication. |
| | 5.2 Is the numerical result being assessed likely to have been selected on the basis of the results from: multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | NI | NI | PN | NI | No concerns with four-stair climb or AEs of treatment. No information about age at loss of ambulation, loss of ambulation, or lung function. |
| | 5.3 Is the numerical result being assessed likely to have been selected on the basis of the results from: multiple eligible analyses of the data? | NI | NI | NI | PN | NI | Efficacy analyses are only presented in the CS for Group A and a post-hoc analysis was conducted in which the company report that results for the overall population are consistent with Group A. Although this was done as planned in the trial protocol, for the purposes of the CS, all data are not presented separately for Group A, Group B, and the overall population, making this difficult to judge. The EAG asked for this in clarification question A4 and A8 but the company did not provide this in full. No concerns with AEs of treatment effect – aligns with protocol and in overall population as everyone ended up receiving treatment. |
| | **Risk of bias judgement** | **Some concerns** | **Some concerns** | **Some concerns** | **Low** | **Some concerns** | **Some concerns with bias in the selection of the reported result because data for efficacy analyses only presented for Group A in the CS. No information on age at loss of ambulation, loss of ambulation or lung function provided in the trial journal article or CS (and age at loss of ambulation not pre-specified in protocol)** |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | **High** | **Some concerns** | **Low** | **High** | |

## 9.4 Appendix 4: Quality assessment results for the OLE study (amended from appendix table 12 of the CS)

| Question | CS assessment (verbatim from CS appendix table 12) | EAG comment |
|---|---|---|
| **Was the cohort recruited in an acceptable way** | Yes, the cohort was recruited from previous peer-reviewed studies,[1, 2, 5, 6] plus an applicable cohort who were applicable for inclusion in the peer reviewed EPIDYS study[1, 2] but were unable to join due to the maximum recruitment numbers being reached | The EAG have concerns about the comparability of the cohort at baseline. The initial recruitment of patients selecting on ambulation as inclusion criteria in EPIDYS and Study 43 introduces concerns into the generalisability of the study's results. Additionally, the differentiation of participants between the "givinostat" and "naïve givinostat" subgroups is not clear, since both groups contain patients with the same inclusion criteria and intervention. |
| **Was the exposure accurately measured to minimise bias?** | Yes, dose exposure was measured for all boys participating in the study. Duration of exposure to study treatment, actual duration, and percent compliance and number and percentage of subjects categorised as compliant (assessed using data from the 'Dosage Compliance' page of the eCRF), were measured and presented by treatment group and overall for the Safety analysis set. Total daily dose of treatment administered by visit, allowing for any dose modifications, was also assessed, both for total daily dose measured in mg, as well as for total daily dose measured in mg per kg | The EAG have concerns about length of exposure not being adequately considered by considering enrolment into OLE as "time zero". |
| **Was the outcome accurately measured to minimise bias?** | Yes, the study is being monitored by the CRO to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements. Clinical monitors are checking completeness, clarity, and consistency of the data recorded in the eCRFs/CRFs for each participant, and adherence to the protocol and to GCP. Audits, independent of and separate from the routine monitoring and quality control functions, are | The EAG have no concerns about outcome measurement for interpreting the results of OLE. |

| | | |
|---|---|---|
| | being carried out as part of the implementation of QA to ensure that the study is being conducted in compliance with the protocol, SOP, GCP, and all applicable regulatory requirements. Additional QA procedures are being performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented | |
| **Have the authors identified all important confounding factors?** | Yes, these are addressed in the EPIDYS and Study 43 exclusion criteria | The EAG notes that exclusion criteria do not control the in-study variability of potential prognostic or modifying baseline characteristic like age, ethnicity, corticosteroid exposure, baseline clinical characteristics, etc.[68-70] This study is not randomised, so any differences between groups could potentially contribute to changes in outcomes observed from baseline, beside givinostat effects. Even though some of these are described in the baseline characteristics, some are not (like VL MFF and other baseline clinical characteristics) |
| **Have the authors taken account of the confounding factors in the design and/or analysis?** | Yes. Exclusion criteria for EPIDYS and Study 43 were developed to avoid confounding factors from other active treatments, significant co-morbidities or clinical factors that could be worsened by givinostat | The OLE study design is insufficient to control for confounding factors, so outcome results cannot be accurately attributed to givinostat effects only. The EAG notes that the OLE study population is not randomised (the randomisation into EPIDYS is lost on entry to the OLE study), so addressing confounding factors into any comparisons was necessary to avoid bias. And in respect of the uITC, the CS considers Study 43 is not suitable due to the potential for confounding by baseline characteristics (which are stated to be different from EPIDYS). While exclusion of participants on other active treatments or with co-morbidities that may affect the outcomes can be helpful in reducing confounding, this may be insufficient. |

| | | |
|---|---|---|
| **Was the follow-up of patients complete?** | The study is ongoing; as off Dec 2021 DCO, no participants were lost to follow-up or had protocol violations. | NA |
| **How precise in terms of confidence intervals and p values are the results** | Because of the nature of the study, only descriptive statistical methods are used for both the primary and secondary endpoints | The EAG agrees that OLE is not intended as a comparative study. However, a number of 'exploratory' outcomes were also specified in the study protocol for 'delayed' vs 'givinostat' and results reported in the CS. As such, the EAG have conducted a risk of bias assessment for these outcomes using the ROBINS-I tool. |

Abbreviations: (e)CRF, (electronic) case report form; CRO, Contract Research Organisation; DCO, data cut off; GCP, Good Clinical Practice; OLE, open-label extension; QA, Quality Assurance; SOP, Standard Operating Procedure. Source: DoF (Sudy 51 Clinical Study Report; Dec 2021 DCO);7 DoF (Study 51 Protocol)

## 9.5 Appendix 4: Risk of Bias assessment using ROBINS-I tool for OLE

Results assessed for LoA

Proportional Hazards Cox Model: Hazard ratio for Loss of Ambulation was [redacted]

Kaplan-Meier curves Figure 27, CS (Figure 5 in EAG report) for givinostat, delayed givinostat and naïve givinostat

| Domain | Signalling question | Figure 27, CS (Figure 5 in EAG report) | Proportional Hazards Cox Model | Comments |
|---|---|---|---|---|
| **Bias due to confounding** | 1.1 Is there potential for confounding of the effect of intervention in this study? | Y | Y | OLE is not a randomised study, so there is a potential for confounding variables to introduce bias. (age, age at start of corticosteroids, ethnicity, corticosteroid exposure, baseline clinical characteristics, VLFF, type of dystrophin mutation) |
| | 1.2. Was the analysis based on splitting participants' follow up time according to intervention received? | N | N | Participants don't switch between interventions (givinostat vs delayed givinostat) |
| | 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | N | N | Figure 5 does not account for any potential confounders. HR estimates control for some potential confounders (baseline value, treatment group, concomitant steroid use, age at baseline) but omits several more. |
| | 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | N | Y | Figure 5 does not account for any potential confounders. HR estimates control for OLE baseline values, but since interventions started prior to OLE enrolment, this is not appropriate, and baselines from the primary study should be used instead. |
| | **Risk of bias judgement** | **Serious** | **Serious** | OLE is not a randomised study, and there are differences in prognostic baseline characteristics between groups that are not adequately controlled for in the analyses. |

| Domain | Signalling question | Figure 27, CS | Proportional Hazards Cox Model | Comments |
|---|---|---|---|---|
| **Bias in selection of participants into the study** | 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? | Y | Y | Selection into the OLE study was dependent on completing the initial trial for patients coming from Study 43 and EPIDYS. |
| | 2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention? | Y | Y | A higher proportion of patients initially assigned to placebo, and therefore assigned to the "delayed givinostat" were enrolled into OLE (58/61 in EPIDYS) , comparing with participants initially assigned to givinostat (101/118 in EPIDYS and 18/20 in Study 43) |
| | 2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | PY | PY | Reasons to drop out from the primary studies could be potentially related with low perceived benefit or side effects, which could also likely impact loss of ambulation. |
| | 2.4. Do start of follow-up and start of intervention coincide for most participants? | N | N | Participants were assigned to their respective interventions, and received them for the duration of their primary studies before starting follow-up in OLE. The start of the intervention for both the 'givinostat' group and 'delayed givinostat' group from the EPIDYS trial was at the time of the randomisation (time zero), yet the follow-up in OLE only starts after the end of the RCT, discarding 18 weeks of follow-up. The start of the intervention for Study 43 participants was when the drug was first initiated at the start of study 43. |
| | 2.5. Were adjustment techniques used that are likely to correct for the presence of selection biases? | N | N | No adjustment techniques discussed |
| | **Risk of bias judgement** | **Critical** | **Critical** | Selection into the OLE study was dependent on completing the initial trial. Start of follow-up and start of intervention don't coincide for patients coming from Study 43 and EPIDYS. No adjustment techniques are mentioned to control for selection bias. |

| | | | | |
|---|---|---|---|---|
| **Bias in classification of interventions** | 3.1 Were intervention groups clearly defined? | PY | PY | It is not clear why "naïve" givinostat was considered a different subgroup to "givinostat", if both had the same inclusion criteria and the same intervention (givinostat treatment from enrolment). |
| | 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | Y | Y | Patients' interventions were defined by their assignment in their original trial |
| | 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | N | N | Patients' interventions were defined by their assignment in their original trial |
| | **Risk of bias judgement** | **Low** | **Low** | Even though the reasons for splitting the givinostat and naïve givinostat are not clear, there are no significant concerns on this domain. |
| **Bias due to deviations from intended interventions** | 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | N | N | Authors report no protocol deviations regarding intervention |
| | **Risk of bias judgement** | **Low** | **Low** | No major concerns for this domain |
| **Bias due to missing data** | 5.1 Were outcome data available for all, or nearly all, participants? | PN | PN | Authors report no patients lost to follow-up after OLE enrolment, although they note there were several missing values because of missed appointments/tests, due in part to COVID-19, it's not clear what is the magnitude and potential impact of this missing data. |
| | 5.2 Were participants excluded due to missing data on intervention status? | N | N | There are not participants with missing data on intervention status |
| | 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | N | NI | There are not participants excluded due to missing data on other variables needed for the analysis on figure 5, no data on the HR analysis. |
| | 5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions? | NI | NI | There is no data on missed appointments by group |

| | | | | |
|---|---|---|---|---|
| | 5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data? | NI | NI | Missing data was imputed depending on cause of missingness, but no evidence was presented to prove robustness of the results. |
| | **Risk of bias judgement** | **Moderate** | **Moderate** | Authors report an unclear amount of missing values, and the imputations methods used to deal with missing data but there is no evidence to prove robustness of the results |
| **Bias in measurement of outcomes** | 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | PN | PN | Outcome is objective and clearly defined. |
| | 6.2 Were outcome assessors aware of the intervention received by study participants? | PY | PY | Some assessments were done under blinding, but most were probably done under open-label status. |
| | 6.3 Were the methods of outcome assessment comparable across intervention groups? | Y | Y | Outcome assessment methods were the same across intervention groups. |
| | 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | PN | PN | Differential misclassification of outcomes not likely. |
| | **Risk of bias judgement** | **Low** | **Low** | No major concerns for this domain |
| **Bias in selection of the reported result:**<br><br>Is the reported effect estimate likely to be selected, on the basis of the results, from... | 7.1. ... multiple outcome *measurements* within the outcome domain? | N | N | There were not multiple outcome measurements to select from |
| | 7.2 ... multiple *analyses* of the intervention-outcome relationship? | N | N | There were not multiple analysis to select from |

| | | | | |
|---|---|---|---|---|
| | 7.3 ... different *subgroups*? | Y | Y | Reasons to split patients in the “givinostat” and “naïve givinostat” are not clear |
| | **Risk of bias judgement** | **Serious** | **Serious** | Reported effect estimate is likely to be selected, on the basis of the results from different subgroups (Reasons to split patients in the “givinostat” and “naïve givinostat” are not clear) |
| **Overall bias** | **Risk of bias judgement** | **Critical** | **Critical** | Critical concerns regarding selection of participants into the study - Start of follow-up and start of intervention don’t coincide for patients coming from Study 43 and EPIDYS, discarding at least 18 weeks of follow-up. There are differences in prognostic baseline characteristics between groups that are not adequately controlled for in the analyses. Reasons to split patients in the “givinostat” and “naïve givinostat” are not clear |

## 9.6 Appendix 5: Risk of Bias assessment using ROBINS-I tool for uITC

Outcome and effect estimates considered in RoB assessment:
Age at LoA: HR 0.19 (95% CI 0.12 to 0.28) (Adjusted robust SE Table 16). Age at NIV: HR 0.19 (95% CI 0.12 to 0.29) (Adjusted robust SE Table 18)
Age at FVC<1L: HR 0.21 (95% CI 0.14 to 0.33) (Adjusted robust SE Table 19)

| Domain | Signalling question | Age at LoA | Age at NIV | Age at FVC<1L | Comments |
|---|---|---|---|---|---|
| **Bias due to confounding** | 1.1 Is there potential for confounding of the effect of intervention in this study? | Y | Y | Y | There are several prognostic and modifying factors (age at diagnosis, age at start of corticosteroids, ethnicity, dystrophin mutation, corticosteroid regime, clinical baseline characteristics) that could potentially induce bias, there is insufficient information on baseline characteristics on UK registry to adequately assess comparability of the groups. |
| | 1.2. Was the analysis based on splitting participants' follow up time according to intervention received? | N | N | N | No. analysis is not based on participant follow up time |
| | 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | N | N | N | Analysis did not control for important confounders. Groups were matched for a single covariate, age at start of corticosteroids. Data for other potential confounding factors were not available for the ECM arm, so the MAIC was based on one variable. Data for age at NIV and age at FVC< 1L was extrapolated from age at LOA without any further controlling |
| | 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | N | N | N | The uITC did not control for any post-intervention variable. |
| | **Risk of bias judgement** | **Serious** | **Serious** | **Serious** | There are several prognostic factors and potential confounders that were not adequately accounted for because complete baseline on the UK registry data was not available |
| **Bias in selection of participants into the study** | 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? | PY | PY | PY | Selection of participants into givinostat arm of uITC |
| | 2.4. Do start of follow-up and start of intervention coincide for most participants? | N | N | N | Start of follow-up for givinostat arm (diagnosis) does not coincide with start of intervention (study enrolment) leading to immortal time bias, where patients needed to remain ambulant from diagnosis to be eligible into this arm. The rate ratio for included outcomes is not expected to be constant over time. |

| Domain | Signalling question | Age at LoA | Age at NIV | Age at FVC<1L | Comments |
|---|---|---|---|---|---|
| | 2.5. Were adjustment techniques used that are likely to correct for the presence of selection biases? | N | N | N | No adjustment techniques discussed |
| | **Risk of bias judgement** | **Critical** | **Critical** | **Critical** | Start of follow-up for givinostat arm (diagnosis) does not coincide with start of intervention (study enrolment) leading to possible immortal time bias |
| **Bias in classification of interventions** | 3.1 Were intervention groups clearly defined? | **Y** | **Y** | **Y** | Intervention groups were defined by having been enrolled in givinostat studies. Patients from the ECM arm belong to a database of patients for whom givinostat was not available. |
| | 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | Y | Y | Y | Intervention groups were defined by having been enrolled in givinostat studies. Patients from the ECM arm belong to a database of patients for whom givinostat was not available. |
| | 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | N | N | N | Intervention groups were defined by having been enrolled in givinostat studies. Patients from the ECM arm belong to a database of patients for whom givinostat was not available. |
| | **Risk of bias judgement** | **Low** | **Low** | **Low** | No major concerns for this domain. |
| **Bias due to deviations from intended interventions** | 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | NI | NI | NI | No data on intervention deviations on the UK registry |
| | **Risk of bias judgement** | **NI** | **NI** | **NI** | There is not enough information to assess this domain |
| **Bias due to missing data** | 5.1 Were outcome data available for all, or nearly all, participants? | **NI** | **NI** | **NI** | There is insufficient information available to assess missing data for all of the arms. It is unclear how missing information was handled for EPIDYS participants who were not enrolled in OLE. Study 43 participants were excluded from the uITC and data were not reported separately for the givinostat arm of the OLE study (EPIDYS and Study 43 combined) |
| | 5.2 Were participants excluded due to missing data on intervention status? | NI | NI | NI | No, not for the givinostat arm in the uITC. But it is not clear how missing data was handled for ECM arm estimated from registry data. |
| | 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | NI | NI | NI | There is insufficient information available to assess missing data for all of the arms. It is unclear how missing information was handled for other variables needed for the analysis |
| | **Risk of bias judgement** | **NI** | **NI** | **NI** | There is not enough information to assess this domain |

| | | | | | |
|---|---|---|---|---|---|
| **Bias in measurement of outcomes** | 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | PN | PN | PN | For age at loss of ambulation in givinostat arm, outcome is objective and clearly defined, and age at NIV and age at FVC<1 were derived from the former, so it is not likely that knowledge of the intervention influenced the outcome measurement. There is no information on outcome definitions on the ECM arm, but since data comes from an observational registry, knowledge of the intervention received is not likely to affect outcome measurement. |
| | 6.2 Were outcome assessors aware of the intervention received by study participants? | Y | Y | Y | Some patients from givinostat arm were assessed for LOA while under randomisation and blinding, however most events happened after blinding had been lifted. For the other outcomes, the analysis to calculate the outcome was done with knowledge of the intervention |
| | 6.3 Were the methods of outcome assessment comparable across intervention groups? | PN | N | N | Definition of loss of ambulation on ECM arm not reported but a recent UK based registry likely to follow UK practice. Definition of ambulation within givinostat arm varied for participants at baseline in EPIDYS and OLE (30 participants were assessed only at start of OLE). Outcome assessment for age at NIV and age at FVC <1L was done using acceleration factors on age at LOA. |
| | 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | NI | PY | PY | No information available for age at LOA. Age at NIV and age at FVC<1L were calculated using the age at LOA estimate. This estimate has been assessed at critical risk of bias, which is introduced on the givinostat arm only. |
| | **Risk of bias judgement** | **Critical** | **Critical** | **Critical** | |
| **Bias in selection of the reported result -** Is the reported effect estimate likely to be selected, on the basis of the results, from... | 7.1. ... multiple outcome *measurements* within the outcome domain? | N | N | N | **There were not multiple outcome measurements to select from** |
| | 7.2 ... multiple *analyses* of the intervention-outcome relationship? | PY | PY | PY | A comparison against CIHRG instead of the UK registry could have been considered, there are not any sensitivity results to show if the analysis selection was done on the basis of the results. |
| | 7.3 ... different *subgroups*? | Y | Y | Y | Only patients coming from EPIDYS and "naïve givinostat" from OLE were included in the givinostat arm, when patients from Study 43, and "delayed givinostat" where also available |
| | **Risk of bias judgement** | **Serious** | **Serious** | **Serious** | It is likely that the reported effect estimate was selected on the basis of the results from different subgroups, and potentially multiple analyses. |
| Overall bias | **Risk of bias judgement** | **Critical** | **Critical** | **Critical** | **Start of follow-up for givinostat arm (diagnosis) does not coincide with start of intervention (study enrolment) leading to immortal time bias. There are several potential prognostic and modifying factors that were not adequately accounted for, because complete baseline on the UK registry data was not available. It is likely that the reported effect estimate was selected on the basis of the results from different subgroups, and potentially multiple analyses.** |

## 9.7 Appendix 6: Cost Effectiveness ROBIS assessment

This appraisal of the systematic review of economic evaluations was conducted with an amended version of ROBIS tool[15] to remove the synthesis domain as this is not relevant to the submission. The EAG's ROBIS assessment was conducted by one reviewer and checked by a second. Any disagreements were resolved by discussion.

| **DOMAIN 1: STUDY ELIGIBILITY CRITERIA** | |
|---|---|
| • Did the review adhere to pre-defined objectives and eligibility criteria? | Y |
| • Were the eligibility criteria appropriate for the scope? | Y |
| • Were eligibility criteria unambiguous? | PY |
| • Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | Y |
| • Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | PY |
| **Risk of bias judgement:** | LOW |
| **Rationale:** | |
| • The protocol was provided in clarification. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES** | |
|---|---|
| 6. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | Y |
| 7. Were methods additional to database searching used to identify relevant reports? | Y |
| 8. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | Y |
| 9. Were restrictions based on date, publication format, or language appropriate? | Y |
| 10. Were efforts made to minimize error in selection of studies? | Y |
| **Risk of bias judgement:** | **LOW** |
| **Rationale:** | |
| • Searches were appropriately conducted and study selection clearly explained. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL** | |
|---|---|
| 6. Were efforts made to minimize error in data collection? | Y |
| 7. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | Y |
| 8. Were all relevant study results collected for use in the synthesis? | PY |
| 9. Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | Y |
| 10. Were efforts made to minimise error in risk of bias assessment? | Y |
| **Risk of bias judgement:** | **LOW** |
| **Rationale:** | |
| • Protocol provided in clarification. No information was provided in the protocol about conduct relating to data extraction (e.g., 'two reviewers etc' as equitable to text on conduct in study selection). Moreover, the text below was unclear | |

| | |
|---|---|
| | *'Numerous parameters related to economic costings and quality of life (QoL) measures will be extracted from identified studies. The specific data extraction fields will be determined based on the studies identified for final inclusion and following further discussion with ITF Pharma.'*<br><br>Whilst reporting in the protocol was sub-optimal, the report in the Company's review aligned with expectations. |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION




**Response to factual accuracy check and confidential information check**

**Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]**
13/03/2005

[Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.]

**Issue 1 Factual inaccuracies**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Page 21: "In response to a clarification question (B17) the company provided justification that this was due to limited data, and due to the HERCULES model, which provided state costs, not separating the extent of ventilation." | In response to a clarification question (B17) the company provided justification that this was due to limited data, and due to the HERCULES ***CPRD study***, which provided state costs, not separating the extent of ventilation. | The response to clarification question B17 describes the limitations of the Project HERCULES CPRD study in relation to providing detail by health state, not the Project HERCULES model. | Thank you. This has been corrected. |
| Page 28: "Results are to be anticipated in October 2026." | Results are to be anticipated in **mid-2028.** | The Company's current estimate is that ULYSSES data will be available in mid-2028. | Thank you. This has been corrected. |
| Page 38: "Part 1: dose was escalated from givinostat 25 mg bid to 50 mg bid." | Part 1: dose was escalated from givinostat 25 mg bid to 50 mg bid **then reduced to 37.5 mg bid.** | To accurately reflect the dose escalation in EPIDYS, aligned with the CS Appendix M.6.2 and CS Appendix Figure 44. | Thank you. This has been corrected. |
| Page 38: "Completed two 4SC assessments with a mean of 8 seconds or less (≤1 second variance)" | Completed two 4SC assessments with a mean of **≤**8 seconds or less (≤1 second variance) | To correct an error and align text with CS Appendix M.1.1 and CS Table 11. | We have edited this for clarity. However, the EAG consider "≤8 seconds" and "8 seconds or less" to be equivalent statements. |

| | | | |
|---|---|---|---|
| Page 38: “Muscle strength evaluated by elbow fixation measured by hand-held myometry” | Muscle strength evaluated by elbow **flexion** measured by hand-held myometry | To correct an error and align to CS Table 12. | This has been corrected. |
| Page 38: “Safety and tolerability (measured by AE collection, laboratory tests, physical examination, vital signs, echocardiogram and spirometry)” | “Safety and tolerability (measured by AE collection, laboratory tests, physical examination, vital signs, **ECG,** echocardiogram and spirometry)” | To include an endpoint that was omitted in the report, and align to CS Appendix M.6.3. | The list has been edited and ECG included as an outcome. |
| Page 40: “The EAG also sought clarification regarding the definition of ‘ambulant’ used in EPIDYS (clarification question A1)16.” | The EAG also sought clarification regarding the definition of ‘ambulant’ used in EPIDYS (clarification question A**2**)16.” | CQ A1 related to ataluren eligibility, and CQ A2 related to the definition of ambulant. | Thank you. This has been corrected. |
| Page 48, Table 8 Time to rise, sec (adjusted 95% CI)* Group A: “(-10.49 to 3.94)” | (-10.**50** to 3.94) | The correct value in CSR Table 36 is -10.497 and has been incorrectly rounded. | Thank you. This has been corrected. |
| Page 48, Table 8, 6MWT, m (adjusted 95% CI)* Group A: “(-12.07 to 31.9)” | (-12.07 to 31.9**8**) | To correct a rounding error and align to value in CSR Table 36. | Thank you. This has been corrected. |
| Page 50: “The company reported that the trial was not modified as a result of the pandemic and an analysis of 4SC data that excluded boys who completed the 72week | The company reported that the trial was not modified as a result of the pandemic and an analysis of 4SC data that excluded boys who completed the 72-week | Identified an error in CS Appendix E2.2 which should read [0.70 to **0.99**] and not [0.70 to 099] | This has been corrected. |

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| assessment outside of the specified window showed similar results to the main analysis (givinostat-to-placebo ratio 0.83 [0.70 to 099]).” | assessment outside of the specified window showed similar results to the main analysis (givinostat-to-placebo ratio 0.83 [0.70 to **0.99**]). | This value should be updated to match the Mercuri 2024 publication, as shown in the edited text. | |
| Page 52: “The only SAE in two or more boys was vomiting. No patients died during the study.” | The only **severe** AE in two or more boys was vomiting. No patients died during the study. | In the CS severe AE and serious AE (SAE) cannot be used interchangeably due to difference in meaning. | This has been corrected. |
| Page 55, Table 10, Time to walk 10 metres (Seconds), Mean (SD) for Naïve givinostat group: “[redacted]” | [redacted] | To correct an error, and align to CSR Table 20. | This has been corrected. |
| Page 55, Table 10, Time to walk 10 metres (Seconds), Mean (SD) for Overall: “[redacted] | [redacted] | To correct an error, and align to CSR Table 20. | This has been corrected. |
| Page 60: “For the overall population (n=207), 317 major protocol deviations were reported.” | For the overall population (n=207), 231 major protocol deviations were reported (one patient could have more than one major protocol deviation). | The Company is not clear where the EAG’s 317 value is derived from. Calculating from the CSR table the EAG cites gives a total of 231 protocol deviations. Importantly, this is *not* the number of patients who had a protocol deviation; patients may have had more than one major protocol deviation. | Thank you. This has been corrected. |

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| Page 67: “The global nature of CINRG DHNS, whilst making it less suitable for estimating natural history baseline, aligns more with the multi-centre international nature of EPIDYS, which only included 8% of patients in the UK.” | The global nature of CINRG DHNS, whilst making it less suitable for estimating natural history baseline, aligns more with the multi-centre international nature of EPIDYS, which only included **8 patients (6.7%)** in the UK | To correct an error, and align to CSR Table 13. | Thank you. This has been corrected. |
| Page 69: “Table 14: Derivation and use of acceleration factors to estimate Kaplan-Meier curves for different outcomes. Reproduced with modifications* from CS, Table 27” | Table 14: Derivation and use of acceleration factors to estimate Kaplan-Meier curves for different outcomes. Reproduced with modifications* from CS, ***Table 26*** | The table heading refers to the incorrect table from the original CS. | Thank you. This has been corrected. |
| Page 69 Table 15: Deflazacort use duration ≥12 months, “79.7%” | Deflazacort use duration ≥12 months, ***81%*** | Aligned with the CS Appendix D.2.8.1 Table 18. The 79.7% comes from Table 24 in the original CS which reflects the proportion of deflazacort use at baseline and not ≥12 months. | This has been corrected (page 70). |
| Page 75: “The EAG also notes that the median age at FVC<1L are different for both the sensitivity analyses and company base-case for the unadjusted givinostat patients. | The median age at FVC<1L are different for both the sensitivity analyses and company base-case for the unadjusted givinostat patients because of the study-specific AFT multiplier | To clarify the methodology behind estimating the age at FVC<1L for patients receiving givinostat, we used a study-specific AFT multiplier based on the comparator study, which | Thank you for the clarification. The EAG have added this to the report on page 76. |

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| This group of patients should be identical in both analyses, so the medians should be identical. It is unclear why they are different, and it suggests that a slightly different subset of givinostat patients may have been included in each analysis.” | applied to age at LOA which varies across these analyses.<br><br>For the base case using UK registry data, the age at LOA for each individual receiving givinostat was multiplied by an AFT of 1.94 (as detailed in Appendix D, Table 15). This resulted in an estimated pre-MAIC weighted median age at FVC<1L of approximately 34.90 years (i.e., 17.97 years * 1.94).<br><br>Similarly, for the CINRG sensitivity analyses, a different AFT of 1.91 was used (i.e., 17.97 years * 1.91), yielding a pre-MAIC weighted median age at FVC<1L of approximately 34.37 years for the givinostat treatment arm. | was applied to the age at LOA. As a result, we would not expect the median age values to be identical across different datasets.<br><br>For the base case using UK registry data, the age at LOA for each individual receiving givinostat was multiplied by an AFT of 1.94 (as detailed in Appendix D, Table 15). This resulted in an estimated pre-MAIC weighted median age at FVC<1L of approximately 34.90 years (i.e., 17.97 years * 1.94).<br><br>Similarly, for the CINRG sensitivity analyses, a different AFT of 1.91 was used (i.e., 17.97 years * 1.91), yielding a pre-MAIC weighted median age at FVC<1L of approximately 34.37 years for the givinostat treatment arm. | |

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| Page 76: “The EAG identified a potential error in the company’s clarification response – the HRs for age at LOA and age at NIV appear to be identical in the sensitivity analysis.” | Given the CINRG DNHS AFT sensitivity analysis consistently applies an acceleration factor to derive age at LOA to the UK registry database then applies the inverse to derive age at NIV for givinostat, it is expected to generate identical hazard ratios for each outcome. | **<u>UK registry</u>**<br>The UK study reports medians separately for patients who stopped and continued steroids and reports separate KM curves for each group. Given this, acceleration factors were estimated and subsequently applied to the stopped and continued steroid cohorts separately. The table below | Thank you for the explanation. The sentence has been deleted from the EAG report (Page 77). |

summarises the data input by treatment and outcome.

| | **Age at LOA for each individual patient / pseudo patient** | **Age at NIV for each individual patient / pseudo patient** |
|---|---|---|
| Givinostat | Age at LOA | AFT1* Age at LOA |
| ECM | $AF2_{stopped}$ * Age at NIV (stopped cohort)<br>$AFT2_{continued}$ * Age at NIV (continued cohort) | Age at NIV |

The AF in each case are calculated using the below formulas

- AF1 = median age at NIV (UK registry - combined cohort) / median age at LOA (UK registry - combined cohort) - based on full predicted KM curve = 1.5024

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| | | • $AF2_{stopped}$ = median age at LOA (UK registry - steroid stopped cohort) / median age at NIV (UK registry - steroid stopped cohort) = 0.666875<br>• $AF2_{continued}$ = median age at LOA (UK registry - continued cohort) / median age at NIV (UK registry - continued cohort) = 0.6609285<br>AF1 is applied to all givinostat patients, but the AFT applied to the UK registry NIV data is marginally different depending on whether a patient stopped or continued steroids, as such it is expected that the generated HRs for each outcome are marginally different.<br><br>**<u>CINRG DNHS derived AFT</u>**<br>For CINRG DNHS AFT sensitivity analysis, identical HR values are not unexpected in this one scenario as both | |

outcomes are estimated from the same initial datasets, and separate medians are not reported for patients who continued and stopped steroid, so the AFs are based on the entire cohort: The table below summarises the data input by treatment and outcome.

| | **Age at LOA for each individual patient / pseudo patient** | **Age at NIV for each individual patient / pseudo patient** |
|---|---|---|
| Givinostat | Age at LOA | AF1 * Age at LOA = (1/AF2) * Age at LOA |
| ECM | AF2 * Age at NIV = (1/AF1)*Age at NIV | Age at NIV |

The AF in each case are calculated using the below formulas

- AF1 = median age at NIV (CINRG) / median age at LOA (CINRG) = 1.368117

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| | | • AF2 = median age at LOA (CINRG) / median age at NIV (CINRG) = 0.7309316<br><br>Therefore, as AF1 = 1/AF2 (0.73 vs. 1.37 in Table 21 of the EAG report), this leads to identical HRs values for the comparison between givinostat and ECM for age at LOA and age at NIV. This assumption can also be tested by scaling event/censor times by any given value for both arms and fitting a cox model.<br><br>**Summary**<br><br>Given the CINRG DNHS AFT sensitivity analysis consistently applies an acceleration factor to derive age at LOA for the UK registry database then applies the inverse to derive age at NIV for givinostat, it is expected to generate identical hazard ratios for each outcome. However, given that UK registry data analysis uses a composite of patients who stopped and continued steroids to estimate | |

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| | | the AFs to generate age at LOA for the UK registry but then uses the combined cohort to estimate NIV for givinostat, it is expected to give marginally different hazard ratio for each outcome. | |
| Page 82: “Disutilities included for caregivers but company assumes no caregiver QALYs are accrued in the ECM arm.” | Increments and decrements (or disutilities) included for caregivers relative to the midway health state. These are applied to the incremental life years in the givinostat arm only. The company assumes no caregiver QALYs are accrued in the ECM arm. | The current description does not reflect the modelling of caregiver HRQoL in the Company base case.<br>The Company base case includes increments and decrements (or disutilities) relative to the midway health state. Stating that only disutilities are applied mis-represents the approach as the disutility approach seen in the literature. | EAG have made this change. |
| Page 83: “Carer disutility included.” | Carer HRQoL included. | The current description does not reflect the modelling of caregiver HRQoL in the Company base case.<br>The carer disutility approach was not applied in the base case. Nor were disutilities | EAG have made this change. |

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| | | consistently applied e.g., increments were applied to improved health states in the Company base case. | |
| Page 84: “The HERCULES structure was used in both the ataluren and vamorolone appraisals in DMD” | The HERCULES structure was used in the vamorolone appraisal in DMD. The model was unavailable at the time of the ataluren appraisal. | The Project HERCULES model was unavailable at the time of the ataluren NICE submission. This submission used a partitioned survival structure. Limitations associated with this structure were discussed by the EAG and the Committee, including “The committee also highlighted that the model only included one ambulatory state and that ambulatory states would better capture disease progression”. | The EAG have corrected this statement and written:<br>The HERCULES structure was used in the vamorolone appraisal in DMD but was unavailable at the time of the ataluren appraisal.2, 3 In the vamorolone appraisal, both the EAG and committee found the model structure appropriate for decision making. The ataluren model captured LOA as the key clinical milestone. The EAG and committee found the model to be appropriate but EAG critiqued excluding the transfer health state and committee critiqued for not differentiating between early and late ambulatory health states. They do not appear to critique it for having a smaller number of non-ambulatory health states. However, these limitations of |

<table>
<tr><td></td><td></td><td></td><td>the ataluren model are addressed by the HERCULES structure.</td></tr>
<tr><td>Page 86: “following the BNF, prednisone is assumed administered orally as 0.75 mg/kg daily and deflazacort administered orally as 0.90 mg/kg daily”</td><td>Following the BNF, prednisone is assumed to be administered orally as 0.75 mg/kg and deflazacort administered orally as 0.90 mg/kg. In terms of dosing schedule, as per EPIDYS, 82.1% are assumed to receive a daily schedule and 17.9% are assumed to receive an intermittent schedule reflecting 10-days on and 10-days off i.e., half the dose of those patients receiving the daily schedule.</td><td>The CEM does not assume daily dosing for all patients.</td><td>EAG have made this change.</td></tr>
<tr><td>Page 92 Table 27:<table><tr><th></th><th>Landfeldt et al 2023</th></tr><tr><td>Early ambulatory</td><td>0.65</td></tr><tr><td>Late ambulatory</td><td rowspan="2">0.49</td></tr><tr><td>Transfer</td></tr><tr><td>HTMF, no ventilation</td><td rowspan="2">0.31</td></tr><tr><td>No HTMF, no ventilation</td></tr><tr><td>HTMF, night-time ventilation</td><td>0.26</td></tr></table></td><td><table><tr><th></th><th>Landfeldt al. 2014, 2016</th></tr><tr><td>Early ambulatory</td><td>0.70</td></tr><tr><td>Late ambulatory</td><td>0.61</td></tr><tr><td>Transfer</td><td>0.61</td></tr><tr><td>HTMF, no ventilation</td><td>0.22</td></tr><tr><td>No HTMF, no ventilation</td><td>0.22</td></tr><tr><td>HTMF, night-time ventilation</td><td>0.22</td></tr></table></td><td>The utility values in Table 27 do not align with the patient utility values applied in the scenario using Landfeldt et al. within the CS. It is unclear where the values are from in the EAG’s table.</td><td>We have now updated the report to clarify these EQ-5D values were available from the Landfelt 2023 paper. These pertain to the same cohort of patients from which the HUI values were obtained for use in one of the CEM’s scenarios.</td></tr>
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<tr>
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<tr><td>No HTMF, night-time ventilation</td><td></td></tr>
<tr><td>Full-time ventilation</td><td></td></tr>
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<table>
<tr><td>No HTMF, night-time ventilation</td><td>0.15</td></tr>
<tr><td>Full-time ventilation</td><td>0.15</td></tr>
</table>
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<td>Page 93 Table 28:
<table>
<tr><th>Health States</th><th>BOI values applie</th></tr>
<tr><td>1 - Early ambulatory</td><td>-0.203</td></tr>
<tr><td>2 - Late ambulatory</td><td>-0.253</td></tr>
<tr><td>3 - Transfer</td><td>-0.343</td></tr>
<tr><td>4 - HTMF, no ventilation</td><td>-0.363</td></tr>
<tr><td>5 - No HTMF, no ventilation</td><td>-0.423</td></tr>
<tr><td>6 - HTMF, night-time ventilation</td><td>-0.383</td></tr>
<tr><td>7 - No HTMF, night-time ventilation</td><td>-0.413</td></tr>
<tr><td>8 - Full time ventilation</td><td>-0.443</td></tr>
<tr><td>9 - Death (bereavement - all deaths)</td><td>-0.923</td></tr>
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<table>
<tr><th>Health States</th><th>Values applied (calculated from study)</th></tr>
<tr><td>1 - Early ambulatory</td><td>0.16</td></tr>
<tr><td>2 - Late ambulatory</td><td>0.11</td></tr>
<tr><td>3 - Transfer</td><td>0.02</td></tr>
<tr><td>4 - HTMF, no ventilation</td><td>0.00</td></tr>
<tr><td>5 - No HTMF, no ventilation</td><td>-0.06</td></tr>
<tr><td>6 - HTMF, night-time ventilation</td><td>-0.02</td></tr>
<tr><td>7 - No HTMF, night-time ventilation</td><td>-0.05</td></tr>
<tr><td>8 - Full time ventilation</td><td>-0.08</td></tr>
<tr><td>9 - Death (bereavement - all deaths)</td><td>-0.56</td></tr>
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</td>
<td>The Company CS does not include BOI values for caregiver utilities within the CEM. The values presented in Table 28 are disutility values which are calculated from the Pfizer vignette study and applied in a scenario analysis only. In line with the table heading, this table should compare the EAG preferred BOI values from the vamorolone NICE submission with the values applied in the base case CS. Of note, there is nowhere currently in the EAG report where it is clarified which values are applied in the Company base case, nor how these are applied e.g., to the incremental change caused by givinostat.</td>
<td>The company's base case is not directly comparable to EAG’s because the methods preferred excludes caregiver QALYs on ECM arm. A scenario in which the CEM applies the disutilities approach to both treatment and ECM arms, using their BOI study decrements relative to general population is compared to EAG’s disutilities approach using BOI Study decrements from TA1031committee.</td>
</tr>
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<td>Page 94: “The EAG notes 0.8% of patients in the EPYDIS study participants (Table 33 of CS) experienced Spinal fracture.”</td>
<td>The EAG notes 0.8% of patients in the EPIDYS study participants in the givinostat arm (Table 33</td>
<td>This percentage relates to the participants in the givinostat arm and not all patients in EPIDYS.</td>
<td>Thank you. This has been corrected.</td>
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</table>

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| | of CS) experienced Spinal fracture. | Additional spelling error of EPIDYS. | |
| Page 95 Table 29: Incremental QALYs w/ severity modifier = 6.8 | 6.8 + 9.2 = 16 | In the EAG's approach where the severity modifier is only applied to patient incremental QALYs, the unadjusted caregiver incremental QALYs should still be added to the total incremental QALYs. | Thank you. This has been corrected. Furthermore, details of the calculation have been added to section 7 along with a table showing the total incremental QALYs with and without the severity modifier applied for the EAG's preferred assumptions. |
| Page 96 Table 30: Month 6+ Company scenario = £69.64 | £70.33 | Aligned with the CEM and the CS. | Thank you. This has been corrected. |
| Page 110: "The impact on later transitions is due only to delayed LOA" | The impact on later ***outcomes*** is due only to delayed LOA | In the EAG scenario there is no impact on later transitions, there is an impact on longer term outcomes. However, due to the assumptions made on the hazard ratios applied to the transitions, the transitions will remain the same as in the ECM arm. | The EAG agrees with this correction and have edited throughout to "The impact on later health state occupancy (i.e., outcomes) is due only to delayed LOA." |

**Issue 2 Wording changes to clarify**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Page 13: "Overall, the technology is modelled to affect QALYs by:<br>• Delaying loss of ambulation and thus progression to more severe states of DMD with only hand to mouth function and increasing use of ventilation<br>• Reducing the impact on caregivers" | Overall, the technology is modelled to affect QALYs by:<br>• Delaying loss of ambulation and thus progression to more severe states of DMD with only hand to mouth function and increasing use of ventilation, ***and death***<br>• Reducing the impact on caregivers | Givinostat is not anticipated to directly impact survival. However, it is anticipated that extended time to LOA, NIV, and FVC<1L will indirectly impact survival. | The EAG agrees with this rewording and have made the suggested change. |
| Page 13: "Overall, the technology is modelled to affect costs by:<br>• Incurring treatment costs, monitoring costs, and administration costs<br>• Reducing costs from use of ventilation" | Overall, the technology is modelled to affect costs by:<br>• Incurring treatment costs, monitoring costs, and administration costs<br>• Reducing costs from ***co-morbidities (e.g., spinal fusion surgery) and*** use of ventilation | As givinostat delays the time to LOA, it is anticipated that givinostat will reduce costs associated with co-morbidities relating to non-ambulant status. Within the CEM, the costs of spinal fusion surgery associated with scoliosis are reflected. | EAG have made this change. |

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| Page 17: “These additional factors are very important prognostic factors, and their impact on the results after weighting is to attenuate the effect of givinostat versus ECM on age at LOA (and subsequently on age at NIV and age at FVL <1L). | No specific amend suggested but the Company requests that the EAG clarifies how they defined the factors as “very important” | Amend requested to provide greater transparency on the evidence supporting EAG statements. | This is not a factual inaccuracy. |
| Page 18: “Furthermore the EAG believe that CINRG DHNS may be more closely balanced to EPIDYS/OLE in terms of other unobserved prognostic factors than the UK registry study.” | No specific amend suggested but the Company requests that further information on “unobserved prognostic factors” should be specified | The EAG report implies that there are multiple prognostic factors which are not observed in the datasets. If the EAG believes there are imbalances between the groups, this should be stated clearly based on specific prognostic factors. Otherwise the report as written implies that there are differences between the groups which are impossible to disprove | This is not a factual inaccuracy. |
| Page 22: “The EAG explored calibration to the best available survival estimates at ages 10, 20, 30, and 40, and also to UK real world data on median age starting | No specific amend suggested but the Company requests that further information on the “best available survival estimates” is provided | Amend requested to provide greater transparency on the evidence supporting EAG statements. | This is not a factual inaccuracy. |

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| ventilation (18.1 years) and starting full time ventilation (20.5 years).” | | | |
| Page 29: “The omission of ataluren is considered as a key issue and incorporated in Key Issue 1.” | The consideration of ataluren as a comparator is incorporated in Key Issue 1. | The text as written implies that it is the omission of ataluren that is the Key Issue. This is not the case as the EAG itself concludes that exclusion of ataluren is appropriate. It would be clearer to use the suggested wording. | The EAG do not consider this to be a factual inaccuracy. The NICE scope states that ataluren is a comparator for the appraisal. Ataluren was not included as a comparator in the STA and the choice of comparators are considered a Key Issue. |
| Page 78: “These hazard ratios capture *exactly the same mechanism for the treatment effect* due to the way in which they are derived (from age at LOA in givinostat patients, using acceleration factors), and so applying them to all transition probabilities likely overstates the efficacy of givinostat.” | These hazard ratios capture *exactly the same mechanism for the treatment effect* due to the way in which they are derived (from age at LOA in givinostat patients, using acceleration factors), and so applying them to all transition probabilities likely overstates the efficacy of givinostat – as acknowledged in the CS. | We have been transparent about the challenges of applying the hazard ratios within the Project HERCULES model structure. We avoided applying the estimated hazard ratios from the indirect comparisons within the CEM to avoid these limitations. As described in the CS, we used the median values from the indirect comparisons and calibrated the hazard ratios applied in the CEM to align the model outcomes with the outcomes from the indirect comparisons. We believe that | This is not a factual inaccuracy. |

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| | | this approach avoids the potential for double counting the efficacy of givinostat. | |
| Page 84: “It is also aligned with the committee conclusion on the NICE appraisal of vamorolone for treating DMD (TA1031).” | It is also aligned with the committee conclusion on the NICE appraisal of vamorolone for treating DMD (TA1031). The Committee for the NICE appraisal of ataluren considered the impact on caregivers in its decision making in a qualitative way. | Both the vamorolone and the ataluren NICE submissions highlight the caregiver burden in DMD and the relevance of considering caregiver HRQoL in its decision making. However, the ataluren committee decided to consider the impact on caregivers qualitatively. | The EAG agrees with this rewording and have made the suggested change. |
| Page 92: “The two studies explored in scenarios by the company have also been used in TA1031, and that preferred by the relevant EAG was the burden of illness (BOI) study informed by a Delphi panel, which measured quality of life for patients and caregivers in the UK using EQ-5D as part of Project HERCULES. The EAG follows this recommendation to use the BOI study to inform health state utilities in the givinostat cost-effectiveness model as it is set in the UK and uses EQ-5D.” | The two studies explored in scenarios by the company have also been used in TA1031, and that preferred by the relevant EAG was the burden of illness (BOI) study informed by a Delphi panel, which measured quality of life for patients and caregivers in the UK using EQ-5D as part of Project HERCULES. Although, the EAG noted that there were limitations with both sources of utility values. The committee agreed with the EAG that both sources of utility values had | The wording implied that the EAG and the Committee did not have concerns about the BOI study. This was not the case and the study was heavily criticised throughout the appraisal. The BOI study was selected as being preferable to Landfeldt et al. as it closely matched the health states in the natural history model. | Thank you, the information has been added. |

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| | limitations. The committee concluded that uncertainties still remained around the most appropriate source of utility values. The committee preferred to use the utility values from the BOI study. This was because they most closely matched the health states in the natural history model, despite the uncertainties.<br><br>The EAG follows this recommendation to use the BOI study to inform health state utilities in the givinostat cost-effectiveness model as it is set in the UK and uses EQ-5D. | | |
| Page 93: “The EAG rectified inaccuracies in modelling the quality of life of caregivers.” | The EAG updated the approach to modelling the quality of life of caregivers. | In line with the EAG’s comments throughout the report, no errors were identified or corrected within the CEM. This statement relates to an alternative approach to modelling caregiver HRQoL, rather than correcting the company approach. | EAG have made this change. |

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| Page 93: “The company did not calculate caregiver QALYs for the ECM arm and did not provide a reasonable justification for not doing so in response to clarification B13.” | The company did not calculate caregiver QALYs for the ECM arm and the EAG do not consider their justification in response to clarification B13 reasonable. | The approach in the CS aims at modelling only the impact on caregiver HRQoL from givinostat, rather than characterising the burden of HRQoL in both the ECM and givinostat arms. This was suggested by the original EAG at the Decision Problem Meeting and the methodology has been applied (and accepted by an EAG) in another NICE submission. This information was provided in the response to clarification B13. | The EAG agrees with this rewording and have made the suggested change. |
| Page 93: “The company apply a bereavement disutility for dead patients but in response to clarification B.14 do not provide sufficient evidence.” | The company apply a bereavement disutility for the incremental LYs in the givinostat vs. ECM treatment arms. As givinostat accrues more LYs than ECM, this becomes a positive QALY gain which is only applied for the additional LYs accrued by givinostat relative to ECM. | The response to clarification B14 has not been summarised within the EAG’s report. Whilst this may be interpreted as a bereavement decrement, it is not applied in the conventional approach i.e., it is not applied for the full model time horizon and reflects the benefit of extended survival on caregivers. This nuance is important for assessing the | The EAG has not made this change. No new information because evidence to support a claim for extended survival not received from any of the company’s clinical studies, or statistical analyses. |

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| | | validity of the company approach. | |
| Page 93: “Although the company present three alternate methods accounting for caregiver HRQoL, in clarification response B15 they find substantial uncertainty concerning the choice of an appropriate method” | Although the company present three alternate methods accounting for caregiver HRQoL, in clarification response B15 they find substantial uncertainty concerning the choice of an appropriate method in terms of how QALYs are accrued over time. | The differences between the approaches are due to how the QALYs are accrued across the health states. However, there is not substantial uncertainty across the results from the methods – as described in the CS, all methods produce the same total caregiver QALY impact. | The EAG have added this clarification. |
| Page 104: “This aligns with the position stated by the company in Company Submission Section B.3.8 and B.3.3.4, and reiterated in response to clarification questions B3 and B4.” | Remove statement. | As detailed in Section B.3.8 and B.3.3.4 in the CS and B3 and B4 of the clarification questions, no direct treatment effect is assumed beyond loss of ambulation for givinostat. However, this is a misquote from the EAG. The statement preceding this statement: “This assumes that givinostat only has a treatment effect on LOA (i.e., transition from State 2 (Late ambulatory) ("Patient cannot stand from supine but can walk/run 10mt") to State 3 (Transfer) ("Patient no longer | As agreed by the EAG elsewhere, these statements have been amended. In this specific instance to:<br>“This assumes that givinostat only has a treatment effect on LOA (i.e., transition from State 2 (Late ambulatory) ("Patient cannot stand from supine but can walk/run 10mt") to State 3 (Transfer) ("Patient no longer has the ability to walk or stand from supine but is able to stand assisted")) **and that the impact on later health state occupancy (i.e., outcomes) is due only to delayed LOA.** This |

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| | | has the ability to walk or stand from supine but is able to stand assisted")) and that the impact on later transitions is due only to delayed LOA." does not align with the Company's position for two reasons: (1) givinostat is also anticipated to have a treatment effect from State 1 to State 2 in the model and (2) givinostat is anticipated to have indirect effects on longer-term outcomes. Nowhere in the CS has the Company stated that there would be no treatment effect from health State 1 to State 2. Additionally, we have assumed that there is a longer term indirect effect driven by the improvement in short term outcomes. | aligns with the position stated by the company in Company Submission Section B.3.8 and B.3.3.4, and reiterated in response to clarification questions B3 and B4." |
| Page 109: "In clarification question B13 the company argued against including caregiver QALYs on the ECM arm but including on givinostat as the impact on the latter was not well understood and required exploration" | Remove statement. | Whilst we have acknowledged the challenges associated with modelling caregiver HRQoL in our CS and our responses (B13), we have not argued against including caregiver QALYs on the ECM arm | The EAG have rephrased to:<br><br>"Caregiver QALYs are included on both the givinostat and ECM arm. The company included caregiver QALYs only on the givinostat arm. |

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| | | because they are not well understood, nor because they required exploration. | The EAG argues this does not give a fair exploration of the impact of caregiver QALYs on givinostat as the incremental caregiver QALYs are not estimated." |
| Page 128:<br>No details in CS for loss of ambulation (pre-specified outcome) but descriptive results for this outcome are presented in the main journal publication and likely appropriate. | Remove statement | Loss of ambulation in EPIDYS is covered in the CS on page 113, "One boy, who was receiving placebo, lost ambulation at Week 60.[22, 132]" and on page 124, "The enrichment was effective, with only one boy (receiving placebo) losing ambulation." | The EAG have added a clarification to the table (now page 133). However, the EAG's assessment of RoB is unchanged for loss of ambulation (it is 'low' risk) since the Mercuri journal publication had already been used as the source of information for EPIDYS.<br>The EAG note that the ambulatory outcomes were reported in section 2.6 alongside other clinical effectiveness outcomes for the EPIDYS 'target ITT' population (Group A). The statement on page 113 of the CS is reported in section 2.9, alongside 'adverse reactions'. For adverse events/ safety outcomes the CS uses the |

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| | | | overall ITT population (Group A and B). |
| Page 139: “Data for other potential confounding factors were not available for the ECM arm, so could the MAIC was based on one variable.” | No specific amend is suggested but the sentence is currently unclear i.e. “so could the MAIC was based on one variable” | Grammatical (sense error). | Corrected |

**Issue 3 Spelling or grammatical errors**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Page 17: “FVL<1L” | FV***C***<1L | Spelling error. | Corrected |
| Page 36: “Kaplan-Maia” | Kaplan-M**eier** | Spelling error. | Corrected |
| Page 41: “off target” | Off**-**target | Typographical error. | Hyphen added, but not capitalised |
| Page 43: “In response to clarification question A6, the company provided the proportion of participants recruited pre- and post-protocol amendment.16 The groups were small (pre-change n=58, post change n=62) but reasonably balanced and, coupled with the CS subgroup analyses, the EAG agrees that there is no evidence to suggest dose regimen modified treatment effect (see EAG report section **Error! Reference source not found.**). “ | Remove duplicated text from document | Duplicated text. | Corrected |
| Page 44: “78.7%%” | 78.7% | Typographical error. | Corrected |
| Page 49: “(95% CI −1.41, 7.33; p=0.1824)).” | (95% CI −1.41, 7.33; p=0.1824) | Typographical error. | Corrected |

| | | | |
|---|---|---|---|
| Page 65: “FEV<1L” | F***V***C<1L | Spelling error. | Corrected |
| Page 75: “FVC>1L” | FVC**<**1L | Spelling error. | Corrected |
| Page 77: “month)s” | ***Months)*** | Spelling error. | Corrected |
| Page 78: “bewteen” | ***Between*** | Spelling error. | Corrected |
| Page 79: “()” | Remove | Spelling error. | Parentheses were missing a section cross-reference. Corrected. |
| Page 85: “EPYDIS” | EPIDYS | Spelling error. | Corrected |
| Page 86: “Ambulator” | Ambulatory | Spelling error. | Corrected |
| Page 92: “of lack” | Lack of | Spelling error. | Corrected |
| Page 95: “Iin” | In | Spelling error. | Corrected (page 104) |
| Page 95: “SoC” | ECM | Spelling error. | Corrected |
| Page 103 and 104: “CINRGH” | CINRG | Spelling error. | Corrected |
| Page 139: “Data for other potential confounding factors were not available for the ECM arm, so could the MAIC was based on one variable.” | Please amend the text | Grammatical (sense error). | Corrected (page 144) |

**Issue 4 Confidential markup**

| Location of incorrect marking | Description of incorrect marking | Amended marking | EAG response |
|---|---|---|---|
| Throughout the document | We understand that text marked for redaction in teal blue highlight should also be underlined as per Section 5.4.18 of the Guidance linked to at the start of this document. “Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual). | [redacted] | Thank you. This has been corrected and teal text has also been underlined. |
| Page 55 Table 10 | Please un-redact the following [redacted] | 6-minute walking distance (6MWT) (metres), Mean (SD)<br>NSAA score, mean (SD)<br>4-Stair Climb (4SC) (Seconds), Mean (SD)<br>Time to walk 10 meters (Seconds), Mean (SD)<br>Time to rise from floor (Seconds), Mean (SD) | Thank you. This has been corrected. |

(Please add further lines to the table as necessary)

# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Tuesday 6 May 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# About you

**Table 1: About you**

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | ITF Pharma UK (Company respondent) |
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | N/A |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry | None |

# Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the EAR.

**Table 2: Key issues**

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| 1. Have comparators been appropriately specified in the submission? | No | Yes, the comparator has been appropriately specified. Established clinical management (ECM) is the only relevant comparator to givinostat.<br>Ataluren is not an appropriate comparator for givinostat in this appraisal as it is used in a very small sub-population of patients with Duchenne muscular dystrophy (DMD) and its future use in the UK is very uncertain. The Evidence Assessment Group (EAG) agrees with this. The European Commission confirmed its decision not to renew the conditional marketing authorisation for ataluren in the European Union on 28 March 2025, as the effectiveness of the medicine had not been confirmed.[1]<br>While prednisone and deflazacort are included as comparators, vamorolone was not accepted or widely used at the time of scoping and was only approved during our submission process. Moreover, the efficacy of vamorolone remains uncertain – this was a key point of discussion during its ACM – and its impact on the natural history model for ECM, or when used in combination with givinostat, is unknown. Importantly, vamorolone would be used alongside givinostat rather than instead of it, meaning it would be included in both treatment arms. As a result, it is not displacing the use of givinostat in the treatment pathway, and its inclusion would likely have minimal impact on the relative treatment effect. The company expects that boys and young men initiating givinostat will continue receiving some form of systemic corticosteroid therapy, which may include prednisone, deflazacort, or vamorolone. |
| 2. Definition of 'ambulant' status and implications for generalisability to UK clinical practice | No | Loss of ambulation (LOA) is a gradual change that occurs over time, rather than a clear-cut binary outcome. Typically, boys increasingly lose the ability to mobilise, starting with impaired/loss of ability to run, hop, jump, rise from the floor and climb stairs – followed by needing assistance from other people or mobility aids to walk short distances. Boys transition gradually to wheelchair dependence – initially for longer distances only, and eventually all the time. This gradual progression and variation of ability within and between individuals means that there is no agreed definition of ambulatory status in DMD. However, specific definitions must be used within the constraints of clinical trial inclusion and exclusion criteria and assessment of outcomes. The definitions of ambulatory used in the givinostat studies fall within spectrum of definitions used in clinical practice, and clinical experts have confirmed that the definitions used are appropriate. These include the definition from North Star data collection forms, |

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|---|---|---|
| | | which define ambulant as being able to walk 10 metres without assistance (and non-ambulant as not being not able to walk 10 metres without assistance). Furthermore, the givinostat trials definitions align with that used in the long-term Phase 3 study of ataluren (Study 019) where LOA was defined as a boy consistently taking more than 30 seconds to run/walk 10 metres.[2]<br>In EPIDYS, LOA is defined as any boy/young man who satisfies both of the following criteria at the same visit at any point prior to or at the end of the study and continues to satisfy the criteria at all subsequent visits to the end of the study:<br>• Boy/young man is unable to perform the 6-minute walking test (6MWT) due to physical inability<br>• Boy/young man is unable to complete the 10-metre walk/run test (10MWT) in 30 seconds or less without any support or devices (10MWT grading ≤2).<br>Study 51 definition of non-ambulant boys/young men:<br>• Unable to complete the 10MWT in 30 seconds or less without any support or devices. |
| 3. *Post-hoc* selection of givinostat OLE patients | Yes | As described in Section B.2.8.1 of the CS and in Clarification Questions (CQ) A14, patients in the two givinostat studies were eligible to be included in the indirect treatment comparisons (ITCs) if they had received givinostat from study entry:<br>• Patients who were randomised to placebo in EPIDYS and who received delayed givinostat in the Open-label extension (OLE) study were excluded given the treatment effect in those patients would be confounded.<br>• Patients who were enrolled in Study 51 but were previously enrolled in Study 43 were excluded due to different inclusion and exclusion criteria and givinostat exposure in Study 43 and EPIDYS.<br>Patients enrolled in EPIDYS who went on to enrol in the OLE study were assessed based on their most recent follow-up to avoid double counting.<br>The EAG note that the *post hoc* selection of givinostat OLE patients is a key issue (Key Issue 3) and suggest a sensitivity analysis that includes all patients from the OLE in the ITCs to resolve this issue. In response to this key issue, we have conducted a sensitivity analysis that includes all patients in the OLE (including those originally enrolled in Study 43) in the ITCs.<br>Whilst these sensitivity analyses have been conducted in response to the EAG's request, the base case analysis, which includes only the givinostat and givinostat-naïve groups from the OLE, is the most robust. These patients met the trials' inclusion and exclusion criteria and received givinostat from baseline – i.e. at the point of initial eligibility. In contrast, patients in the delayed givinostat group also |

met the inclusion and exclusion criteria at trial entry but received placebo during the 18-month EPIDYS period before initiating givinostat in the OLE. Using the start of givinostat in the OLE as a new "baseline" does not eliminate the impact of disease progression or accumulated morbidity during the placebo period. Therefore, even though these patients technically meet the same criteria, they are not clinically equivalent to patients who started treatment at trial entry.

Furthermore, 61 patients were initially randomised to placebo in EPIDYS, but only 58 continued into the OLE (see Figure 2 of CQ responses), meaning the delayed givinostat group includes only those who remained eligible for treatment after 18 months. This introduces a selection bias, as patients had to remain eligible to receive givinostat in the OLE. As a result, this group may appear to respond better, not necessarily because of the treatment, but because only the healthier subset transitioned into the OLE. Including these patients risks underestimating the true treatment effect of givinostat due to their later and potentially less favourable starting point.

In addition, excluding the Study 43 patients enrolled in the OLE from the base-case ITC analysis was considered reasonable by the EAG, given the differences in inclusion criteria, baseline characteristics indicating less progressed disease, and treatment dosing regimen for this study.

For these reasons, these analyses are presented as sensitivity analyses only. However, it is noted that the results show consistent significant benefit for givinostat compared with ECM for all endpoints.

Table A presents the givinostat (unadjusted and weighted) and ECM baseline characteristics for the conducted sensitivity analyses. In line with the original analyses, matching was based on age at start of CS treatment. The effective sample size (ESS) was 151.9, a reduction of around one-third compared with the original sample size of 224 givinostat patients, suggesting reasonable overlap in patient characteristics for age at start of CS treatment.

**Table A: Comparison of baseline characteristics: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**

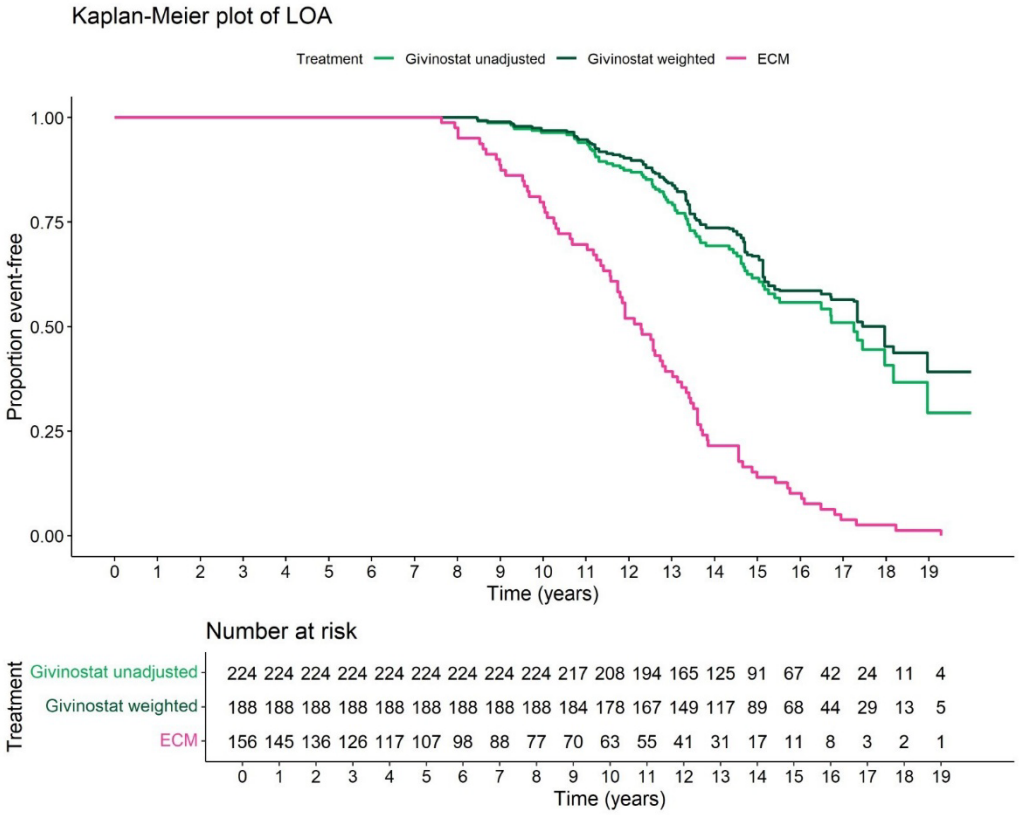
| Treatment arm | N/ESS | CS start age (years) |
|---|---|---|
| Givinostat unadjusted | 224.0 | 5.99 |
| Givinostat weighted | 151.9 | 7.20 |
| ECM | 156.0 | 7.20 |

Abbreviations: CS, corticosteroids; ECM, established clinical management; ESS, effective sample size.

**Age at loss of ambulation**

The Kaplan-Meier (KM) plots for age at LOA for givinostat patients for both unadjusted and weighted patient data, compared with patients receiving ECM (estimated using an acceleration factor) are presented in Figure A.

**Figure A: Kaplan-Meier plot for age at LOA MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**




Abbreviations: ECM, established clinical management; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; OLE, open-label extension; UK, United Kingdom.

Median age at LOA for givinostat treated patients was 17.3 years pre-weighting and 18.0 years post-weighting, compared with 12.3 years for ECM treated patients (Table B). Patients treated with givinostat were significantly older at LOA compared with patients treated with ECM, with HR (95% confidence interval [CI]) of 0.201 (0.142, 0.285) from the weighted comparison with robust SE (Table B). These results are consistent with the base case HR of 0.185 (95% CI 0.121, 0.282).

**Table B: Summary of age at LOA MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**

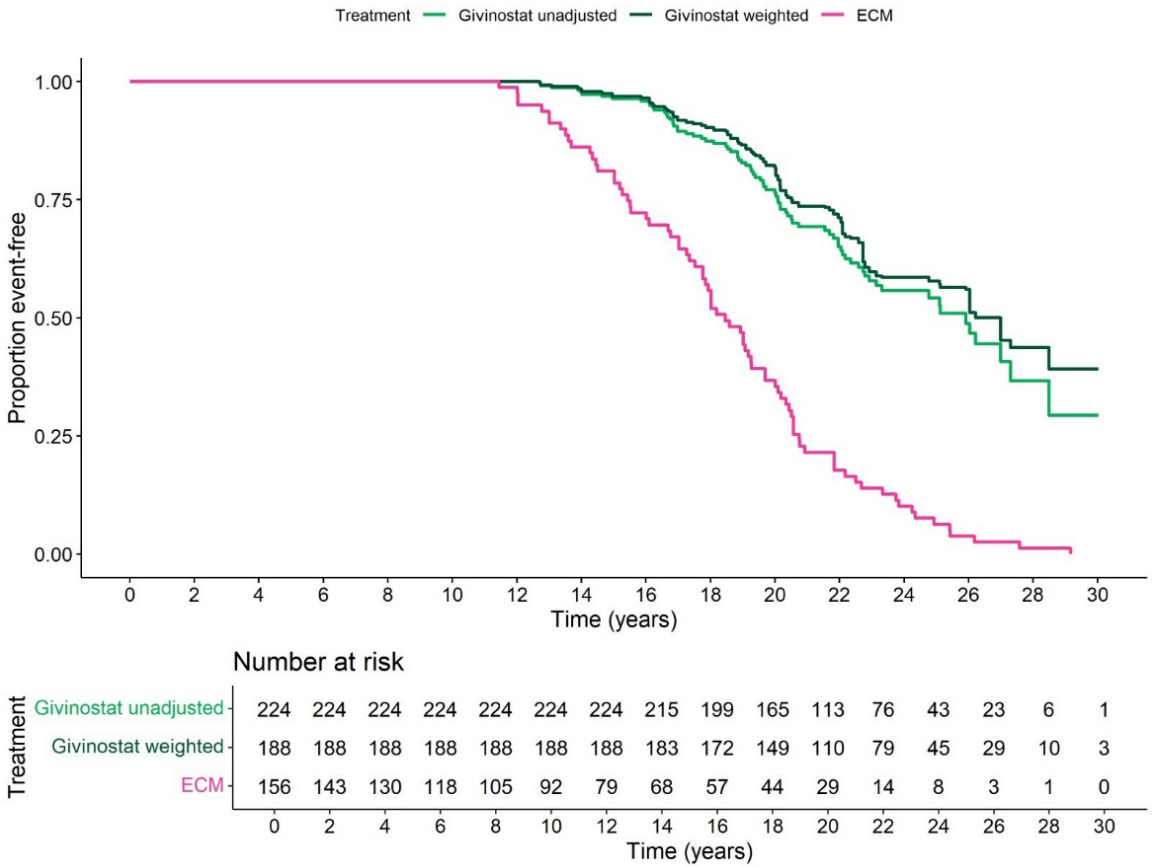
| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (All patients) | 224.0 | 78 | 17.25 (15.40, NE) | **0.241 (0.176, 0.330)** |
| Givinostat weighted (All patients) | 151.9 | 63 | 17.97 (15.26, NE) | Robust SE: **0.201 (0.142, 0.285)** Bootstrap: **0.200 (0.154, 0.263)** |
| ECM (UK real-world data) | 156.0 | 79 | 12.28 (11.74, 13.13) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.

**Age at non-invasive ventilation**

As described in Section B.2.8 of the CS, the estimated acceleration factor was applied to the age at LOA data for patients receiving givinostat. Based on this approach, KM curves estimating the age at NIV for both unadjusted and weighted givinostat patient data, compared with patients receiving ECM, are presented in Figure B.

**Figure B: Kaplan-Meier plot for age at NIV MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**




Abbreviations: ECM, established clinical management; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; UK, United Kingdom.

Median age at NIV for givinostat treated patients was 25.9 years pre-weighting and 27.0 post-weighting, compared with 18.5 years for ECM treated patients (Table C). Patients treated with givinostat were significantly older when receiving NIV, compared with patients treated with ECM with a HR (95% CI) of 0.206 (0.145, 0.293) from the weighted comparison with robust SE (Table C). These results are consistent with the base case HR (95% CI) of 0.190 (0.124, 0.290).

**Table C: Summary of age at NIV MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**

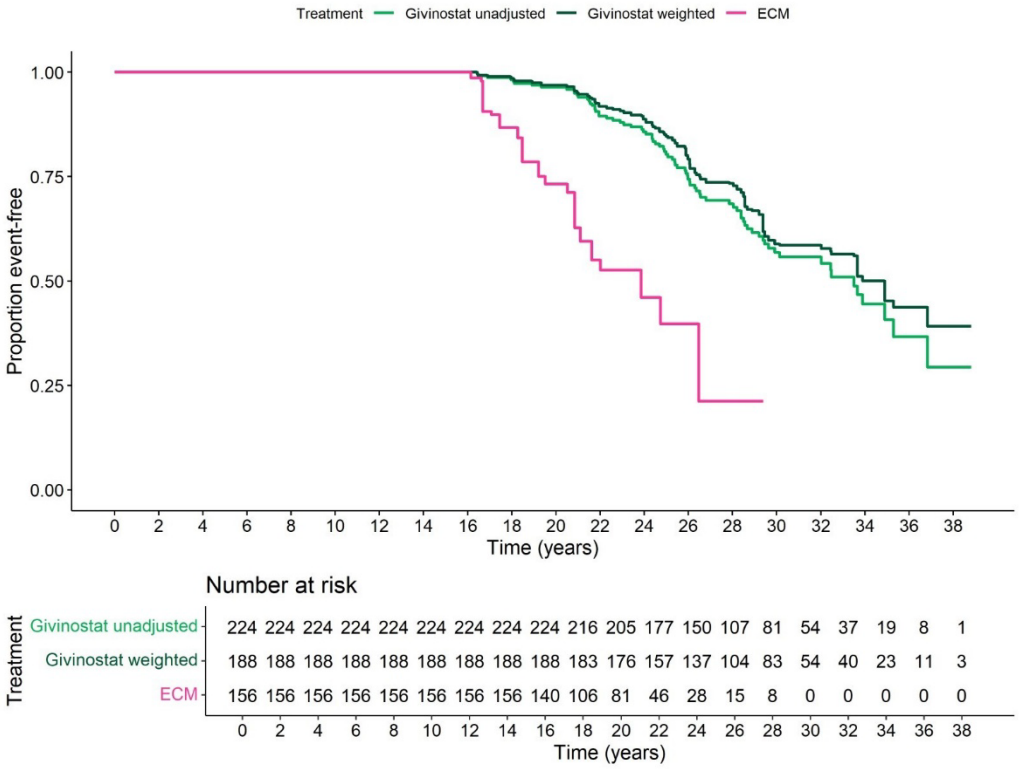
| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. EBM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (All patients) | 224.0 | 78 | 25.92 (23.14, NE) | **0.247 (0.180, 0.338)** |
| Givinostat weighted (All patients) | 151.9 | 63 | 27.00 (22.93, NE) | Robust SE: **0.206 (0.145, 0.293)** Bootstrap: **0.206 (0.158, 0.270)** |
| ECM (UK real-world data) | 156.0 | 79 | 18.46 (17.76, 19.70) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; EBM, established clinical management; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; NIV, non-invasive ventilation; OLE, open-label extension; SE, standard error.

**Age at forced vital capacity <1L**

As described in Section B.2.8 of the CS, the estimated acceleration factor was applied to the age at LOA data for patients receiving givinostat. Based on this approach, KM curves estimating the age at FVC <1L for both the unadjusted and weighted givinostat patient data, compared with patients receiving ECM, are presented in Figure C.

**Figure C: Kaplan-Meier plot for age at FVC <1L MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**




Abbreviations: 1L, 1 litre; FVC, forced vital capacity; MAIC, matching-adjusted indirect comparison.

Median age at FVC <1L for givinostat treated patients was 33.5 years pre-weighting and 34.9 post-weighting, compared with 23.9 years for ECM treated patients (Table D). Patients treated with givinostat were significantly older when reaching FVC <1L compared with patients treated with ECM with a HR (95% CI) of 0.218 (0.149, 0.321) from the weighted comparison with robust SE (Table D). These results are consistent with the base case HR of 0.214 (0.139, 0.329).

**Table D: Summary of age at FVC <1L MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (All patients) | 224.0 | 78 | 33.50 (29.91, NE) | **0.246 (0.173, 0.352)** |
| Givinostat weighted (All patients) | 151.9 | 63 | 34.90 (29.64, NE) | Robust SE: **0.218 (0.149, 0.321)** Bootstrap: **0.217 (0.169, 0.275)** |
| ECM (UK real-world data) | 156.0 | 67 | 23.86 (21.62, 26.47) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: 1L, 1 litre; CI, confidence interval; ECM, established clinical management; ESS, effective sample size; FVC, forced vital capacity; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.

The impact of using the medians from the MAIC sensitivity analyses in the economic model is presented in the scenario analysis under the summary of changes to the cost-effectiveness results. This approach uses the SOLVER methodology as proposed by the Company – see response to Key Issue 11. This scenario is shown to have a limited impact on the updated base case ICER (-1.68%).

In addition, in response to EAG comments, the impact of including the standard deviation (SD) for age at CS initiation in the matching process was considered. The SDs were very similar before adjustment between givinostat and ECM (Table E).

**Table E: Comparison of baseline characteristics across base-case and sensitivity analyses: givinostat vs. ECM (UK real-world data) | Exploring including SD in analyses**

| Treatment arm | Model | N/ESS | CS start age (years) | CS start age SD (years) |
|---|---|---|---|---|
| Givinostat base-case | Unadjusted | 148 | 6.094 | 1.877 |
| Givinostat base-case | Adjusted | 105.1 | 7.197 | NA |
| Givinostat base-case with additional adjustment for SD | Adjusted | 108.2 | 7.197 | 1.896 |
| Givinostat all patients sensitivity analysis | Unadjusted | 224 | 5.991 | 1.910 |
| Givinostat all patients sensitivity analysis | Adjusted | 151.9 | 7.197 | NA |
| Givinostat all patients sensitivity analysis with additional adjustment for SD | Adjusted | 155.7 | 7.197 | 1.896 |
| ECM (UK real-world data) | Unadjusted | 156 | 7.197 | 1.896 |

Abbreviations: CS, corticosteroids; ECM, established clinical management; ESS, effective sample size; SD, standard deviation.

Because of the similarity between the SDs before adjustment, matching for this variable, in addition to mean age at CS initiation, has very minimal impact on the ITC results, as shown in Table F for age at LOA. Thus, the base-case is still considered an appropriate estimate of the relative treatment effect between givinostat and ECM, with the point estimate for the adjusted HR of 0.190 lying well within the 95% CIs from the alternative analyses.

**Table F: Comparison of findings in the base-case and sensitivity analyses for age at LOA: givinostat vs. ECM (UK real-world data) | Exploring including SD in analyses**

| Treatment arm | Model | N/ESS | Events | Median survival (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|
| Givinostat base-case | Unadjusted | 148 | 43 | 17.97 (15.40, NE) | **0.222 (0.153, 0.323)** |
| Givinostat base-case | Adjusted | 105.1 | 36 | NE (23.32, NE) | **0.190 (0.124, 0.290)** |
| Givinostat base-case with additional adjustment for SD | Adjusted | 108.2 | 36 | 17.97 (15.40, NE) | **0.197 (0.131, 0.297)** |
| Givinostat all patients SA | Unadjusted | 224 | 78 | 17.25 (15.4, NE) | **0.241 (0.176, 0.330)** |
| Givinostat all patients SA | Adjusted | 151.9 | 63 | 17.97 (15.26, NE) | **0.201 (0.142, 0.285)** |
| Givinostat all patients SA with additional adjustment for SD | Adjusted | 155.7 | 63 | 17.97 (15.26, NE) | **0.201 (0.142, 0.285)** |

**Bold** text indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SD, standard deviation.

As the differences between the age at LOA comparisons presented in Table F are minimal, and due to the use of acceleration factors when estimating patient outcomes across age at LOA, NIV and FVC <1L (as described in the CS Section 2.8.2), comparisons for age at NIV and age at FVC <1L experience a similarly minimal impact across the alternative ITCs. Consequently, these results are not presented.

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| 4. Source of data to inform comparative treatment efficacy | Yes (see Appendix Tables 1 and 2) | As outlined in the CS Section B.2.8.1, the comparative efficacy estimates were informed by data from the EPIDYS randomised controlled trial (RCT) and the OLE for givinostat, and by published UK real-world data for ECM (i.e. North Star data from three centres presented by Pietrusz[3,4]).<br>In response to EAG feedback requesting greater clarity on the study selection process, Appendix Table 1 provides a topline summary of the rationale for selecting the real-world data sources for the ITC, while |

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| | | Appendix Table 2 outlines the detailed reasons for inclusion or exclusion of each potential source identified through the SLR.<br><br>As described in the response to Key Issue 5, the only head-to-head evidence comparing givinostat with placebo comes from the 18-month EPIDYS trial. While this randomised follow-up period is too short to robustly inform long-term outcomes such as LOA, initiation of NIV, or decline in FVC - which are key components of the economic model - the trial provides valuable evidence of short-term clinical benefit. EPIDYS demonstrated statistically significant improvements in functional endpoints relevant to early disease progression, supporting the potential of givinostat to alter the trajectory of DMD in its earlier stages.<br><br>However, due to the slow, progressive nature of DMD, capturing long-term outcomes in a RCT setting is inherently challenging. Extended follow-up would require many years of observation, during which maintaining a placebo arm may become unethical, and patient retention and treatment crossover become increasingly difficult. Given these constraints, long-term RCTs are not feasible in DMD. In this context, the 18-month randomisation period in EPIDYS is significantly longer than the randomised phases seen in other DMD trials, such as the 12-week randomised phase in the ataluren STRIDE 1 and STRIDE 2 trials,[5,6] and the 24-week randomised phase in the vamorolone VISION-DMD trial.[7]<br><br>While the EPIDYS trial offers high-quality short-term data, using it to inform long-term outcomes would require reliance on surrogate relationships. However, the literature linking early functional outcomes to long-term clinical endpoints in DMD is limited and inconsistent (see response to Key Issue 5). For example, the only study offering a quantitative relationship between a short-term functional outcome (10MWT) and a long-term outcome (LOA) uses a two-year follow-up and stratifies patients categorically ((≤7 seconds vs >7 seconds on 10MWT), rather than modelling a continuous relationship.[8] Moreover, there are few longitudinal datasets that follow patients from early functional decline through to late-stage disease, capturing the necessary clinical and biological variables to robustly establish predictive relationships.<br><br>Further complicating the development of surrogates is the substantial heterogeneity in DMD progression across individuals - driven by factors such as mutation type and genetic modifiers - which limits the generalisability of findings and hampers validation across different study populations. As a result, building surrogate-based extrapolations from EPIDYS data would introduce considerable uncertainty. Nevertheless, in response to Key Issue 5, the Company has provided a summary of the available evidence predicting long-term outcomes from EPIDYS endpoints and demonstrates that, despite limitations, the published literature supports the extrapolations used in the ITCs and economic model. |

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| | | Given these considerations, the UK real-world dataset represents the most appropriate source of long-term data for ECM in the ITCs. Under Key Issue 4, the EAG highlighted several limitations of this approach:<br>• Due to limited availability of baseline characteristics, matching could only be conducted using age at CS initiation, with no ability to adjust for other key prognostic factors or effect modifiers (EAG report, page 68).<br>• Patients enrolled in clinical trials generally have better prognoses than those in routine clinical practice, introducing potential bias when comparing trial populations with registry data, particularly where differences in inclusion/exclusion criteria exist (EAG report, page 68).<br>The EAG expressed a preference for an alternative analysis using the CINRG Duchenne Natural History Study (DNHS) registry, citing the inclusion of two additional matching variables – age at diagnosis and duration of deflazacort use (≥12 months) – as a reason for this preference. While the Company provided this analysis to align with previous methods used in the NICE HST22 appraisal (ataluren), it maintains that the CINRG DNHS dataset is not appropriate to inform the base-case analysis.<br>The CINRG DNHS dataset is outdated and is not comparable to the givinostat data sets. The most recent CINRG data were collected nearly a decade ago and the oldest data are approximately 19 years old (data collection: 2006-2016) and do not align temporally with the EPIDYS, OLE, or UK real-world datasets (data collection: June 2017–February 2022, October 2017–December 2023, and March 2007-October 2022, respectively). The CINRG registry is also comprised of largely North American centres, whereas EPIDYS enrolled a substantially higher proportion of participants from the UK and Europe (including UK) (7.3% and 67.0%, respectively). These regional differences affect patient demographics, standards of care, and clinical outcomes, further limiting comparability.<br>The lack of comparability between the CINRG DNHS and givinostat datasets is highlighted by the substantial reduction in ESS after matching (ESS=37.2), which indicates poor overlap between the CINRG registry and the givinostat trial population. This small ESS has the potential to make the ITC estimates unstable, such that if it were possible to include additional patients in the analysis, the results could be significantly impacted and as such, the robustness and generalisability of any resulting comparative estimates are compromised.<br>The UK real-world data aligns more closely with the givinostat data collected in EPIDYS and the OLE, based on time of data collection and setting. Therefore, this is considered the more robust dataset.<br>The Company recognises the importance of aligning the comparator population with the givinostat trial population for the ITC. However, given the limitations of the CINRG DNHS dataset outlined above and |

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| | | the considerably better clinical relevance of the UK real-world dataset compared with the givinostat data, the Company considers the UK real-world dataset to remain the most appropriate source for informing ECM outcomes within the economic model. |
| 5. Impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints | Yes | As outlined in the response to Key Issue 4, the EPIDYS trial provides the only head-to-head randomised evidence comparing givinostat with placebo. This 18-month trial offers robust data on short-term clinical outcomes and demonstrated statistically significant improvements in functional endpoints relevant to early-stage DMD. These results support the potential of givinostat to modify the course of disease progression.<br>While the randomised follow-up in EPIDYS does not capture long-term outcomes such as LOA, initiation of NIV, or decline in FVC - which are key drivers in the economic model - this limitation is a broader challenge inherent to the clinical development landscape in DMD. The slow and variable nature of disease progression, combined with ethical and practical constraints, makes it difficult to conduct long-duration placebo-controlled trials in this setting. Extended follow-up would require many years, during which issues such as patient retention, crossover, and the ethical acceptability of a long-term placebo arm become increasingly complex.<br>Importantly, the EPIDYS trial includes a substantially longer randomised period than many other DMD studies. For instance, the STRIDE 1 and STRIDE 2 trials of ataluren included only a 12-week randomised phase,[5,6] while the VISION-DMD trial of vamorolone included a 24-week randomised phase.[7]<br>Although EPIDYS offers high-quality evidence on early disease progression, informing long-term outcomes requires extrapolation through surrogate relationships. However, the current literature contains limited and variable evidence linking short-term functional measures to later-stage clinical endpoints in DMD. The disease's heterogeneity, driven by factors such as genotype and individual disease modifiers, further complicates the establishment of generalisable surrogate relationships. As such, building predictive models from EPIDYS data would introduce substantial uncertainty.<br>In response to Key Issue 5, evidence is provided to support the observed outcomes from the EPIDYS trial and the predicted outcomes used in the economic model. While some of these publications were included in the original CS, they are now described in the context of the observed outcomes from EPIDYS to support the predictions of the economic model. Additionally, any new studies published since the time of submission have been included.<br>**Time to run or walk 10 metres (10MWT)**<br>Table G presents the baseline and end of study (EOS) assessments of 10MWT for givinostat and placebo from the EPIDYS study (Table 14.2.7.1.1, CSR). |

**Table G: 10MWT baseline vs. EOS from EPIDYS**

| | Givinostat | Placebo | Difference |
|---|---|---|---|
| Baseline | 5.41 | 5.18 | -0.23 |
| EOS | 6.04 | 7.99 | 1.95 |

Abbreviations: 10MWT, time to run or walk 10 metres; EOS, end of study.

Mazzone et al. (2013) report 24-month longitudinal data in ambulant boys with DMD, identifying predictors of LOA over two years.[8] One key finding is that boys with a 10MWT of ≤7 seconds had a significantly higher risk of losing ambulation, with an odds ratio of 7.9 (95% CI: 2.2–28.3; p=0.002), compared with those with a 10MWT >7 seconds.

Using the EPIDYS EOS (18 months) as a baseline, two years post-EOS corresponds to approximately 3.5 years in the model. At this timepoint, the CEM predicts 94.68% of boys in the givinostat arm remain ambulant. Applying the odds ratio from Mazzone et al. (2013) to the 10MWT distribution in EPIDYS suggests that only 69.2% of boys in the ECM arm would retain ambulation after 3.5 years, compared with 79% predicted by the CEM.[8] This suggests that the model may be overestimating ambulation rates in the ECM arm and, consequently, underestimating the relative treatment effect of givinostat.

These data support the predicted relative treatment effect between givinostat and ECM and suggest that the modelled treatment difference may be conservative.

While Arora et al. (2018)[9] and Duong et al. (2021)[10] do not provide a direct quantitative relationship, both studies offer supportive evidence that the differences observed in the 10MWT between the givinostat and placebo arms at the EOS in EPIDYS are clinically meaningful:

- Arora et al. (2018) present longitudinal data from the ImagingDMD natural history cohort, evaluating timed function tests (TFTs), including 10MWT and 4SC, in boys with DMD.[9] The study reports a high predictive value of 10MWT for subsequent LOA, with an area under the ROC curve (AUC) of 0.93 (95% CI: 0.88–0.97), indicating strong ability of the 10MWT in predicting LOA within one year.
- Duong et al. (2021) assess the minimum detectable change (MDC) and minimal clinically important difference (MCID) in the annual rate of change in TFTs, including 10MWT and 4SC.[10] The study reports statistically significant MDC and MCID values of –0.138 m/sec and –0.212 m/sec, respectively. These results suggest that the observed difference in EPIDYS (mean change of 1.95 seconds) exceeds the threshold for both a real and clinically meaningful change in ambulatory function.

Additional evidence from McDonald et al. (2013, 2024)[11,12] and Bushby et al. (2011)[13] further support the clinical relevance of 10MWT thresholds, showing that times exceeding 10 or 12 seconds are associated with an increased risk of LOA. Although patients in the EPIDYS placebo arm had not yet reached these thresholds at EOS, the trajectory of decline indicated they were likely to do so sooner than those patients in the givinostat arm.

Finally, Humbertclaude et al. (2012) report on a strong correlation between loss of ability to run and age at LOA with an r value of 0.85, p-value <0.0001.[14]

**Time to climb 4 stairs (4SC)**

Table H presents the baseline and EOS assessments of 4SC for givinostat and placebo from the EPIDYS study (Table 20, CSR).

### Table H: 4SC baseline vs. EOS from EPIDYS

| | Givinostat | Placebo | Difference |
|---|---|---|---|
| Baseline | 3.39 | 3.48 | 0.09 |
| EOS | 4.70 | 6.37 | 1.67 |

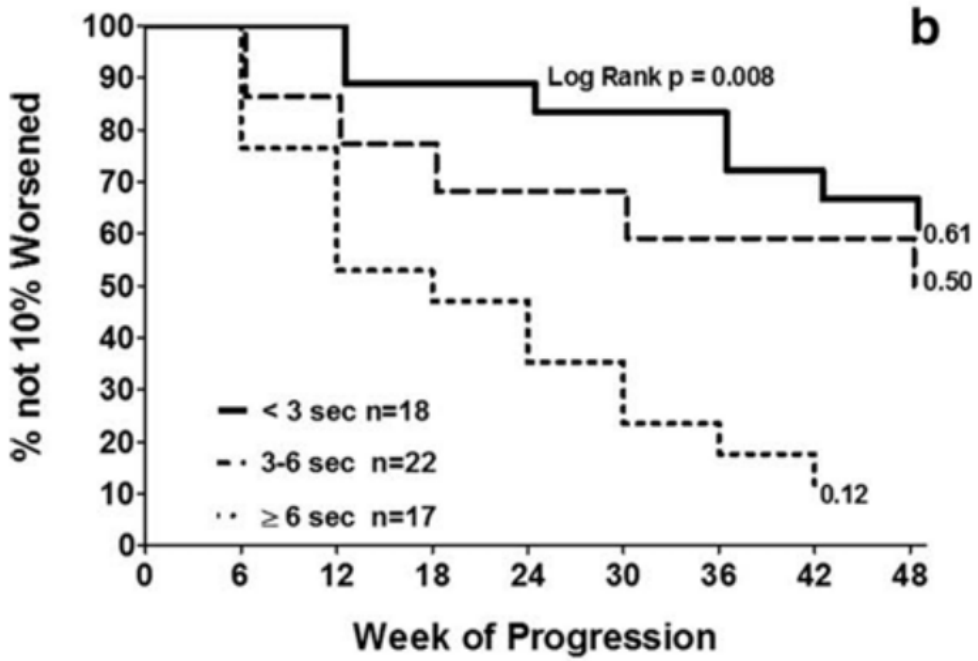
Abbreviations: 4SC, time to climb 4 stairs; EOS, end of study.

While no data were identified providing a direct quantitative relationship, Arora et al. (2018) and Duong et al. (2021) offer supportive evidence that the differences observed in the 4SC between the givinostat and placebo arms at the EOS in EPIDYS are clinically meaningful:

- Arora et al. (2018) report a high predictive value of 4SC for subsequent LOA, with an AUC of 0.96 (95% CI: 0.92–0.99), indicating strong ability of the 4SC in predicting LOA within one year[9]
- Duong et al. (2021) report statistically significant MDC and MCID values of –0.034 task/sec and –0.035 task/sec, respectively.[10] These results suggest that the observed difference in EPIDYS (mean change of 1.67 seconds) exceeds the threshold for both a real and clinically meaningful change in ambulatory function.

Additional evidence from McDonald et al. (2013) further supports the clinical relevance of 4SC endpoints, showing that times <3 seconds, 3–6 seconds, and ≥6 seconds are associated with an increased risk of 10% worsening of disease progression (Figure D).[11]

**Figure D: Relationship between 4SC and % not 10% worsened | McDonald et al. (2013)[11]**




Abbreviations: 4SC, time to climb 4 stairs; sec, seconds.

Finally, Humbertclaude et al. (2012) report on a strong correlation between loss of ability to climb stairs and age at LOA with an r value of 0.84, p-value <0.0001.[14]

**Time to rise from floor (TTR)**

Table I presents the baseline and EOS assessments of TTR for givinostat and placebo from the EPIDYS study (Table 14.2.2.1.1, CSR).

**Table I: TTR baseline vs. EOS from EPIDYS**

| | Givinostat | Placebo | Difference |
|---|---|---|---|
| Baseline | 5.57 | 5.59 | 0.02 |
| EOS | 14.43 | 19.17 | 4.74 |

Abbreviations: EOS, end of study; TTR, time to rise from floor.

While no data were identified providing a direct quantitative relationship, Duong et al. (2021) offer supportive evidence that the differences observed in the TTR between the givinostat and placebo arms at the EOS in EPIDYS are clinically meaningful:

- Duong et al. (2021) report statistically significant MDC and MCID values of –0.026 rise/sec and –0.023 rise/sec, respectively.[10] These results suggest that the observed difference in EPIDYS (mean change of 4.74 seconds) exceeds the threshold for both a real and clinically meaningful change in ambulatory function.

Additional evidence from McDonald et al. (2022)[15] and Zambon et al. (2022)[16] indicate differences in LOA based on TTR. However, the cut-offs they use do not align with the EOS data from EPIDYS. Zambon et al. (2022) show that TTR at baseline was positively associated with age at LOA with a hazard ratio of 1.13 (95% CI: 1.09–1.17).

Finally, Humbertclaude et al. (2012) report on a strong correlation between loss of ability to rise from the floor and age at LOA with an r value of 0.91, p-value <0.0001.[14]

**Weight and height**

Table J and Table K present the baseline and EOS assessments of weight (kg) and height (cm) for givinostat and placebo from the EPIDYS study (Table 70, CSR).

**Table J: Weight (kg) baseline vs. EOS from EPIDYS**

| | Givinostat | Placebo |
|---|---|---|
| Baseline | 31.22 | 32.58 |
| EOS | 33.96 | 37.49 |
| Change from baseline | 2.97 | 4.68 |

Abbreviations: EOS, end of study.

**Table K: Height (cm) baseline vs. EOS from EPIDYS**

| | Givinostat | Placebo |
|---|---|---|
| Baseline | 125.1 | 126.7 |
| EOS | 129 | 131.3 |
| Change from baseline | 3.8 | 4.3 |

Abbreviations: EOS, end of study.

Stimpson et al. (2024) analysed data from 648 boys with DMD treated with glucocorticoids, using 2,228 observations from the UK NorthStar database collected between 2006 and 2020.[17] The research aimed to understand how growth patterns influenced the risk of losing ambulation.

The authors found that the cumulative hazard of LOA was significantly increased by yearly weight standard deviation (SD) gain. That is, a child with a yearly weight gain 0.25SD greater than an average child has a 90% (95% CI 33%–171%) greater risk of LOA. Additionally, reduced height gain, significantly decreased the risk of LOA. Notably, a yearly height stunting of 0.25SD relative to the average height-for-age increase in the non-DMD population was associated with a 74% (95% CI 14%–167%) reduction in risk of LOA.[17] However, it was unclear over what period these reductions in risk were relevant to.

In terms of SDs from EPIDYS, the placebo arm had a weight gain of 1.21SD, while givinostat had a weight gain of 0.82SD. The difference in SDs is 0.39SD. Therefore, this meets the 0.25SD threshold. The placebo arm had a height change of 1.37SD, while givinostat had a height change of 1.18SD. The difference in SDs is 0.19SD. Whilst these data do not yet meet the threshold, the data are trending as supportive for givinostat.

Earlier data presented by Stimpson et al. (2022) supported a relationship between growth patterns and LOA.[18] However, the relationship was less pronounced, for ambulant boys between the ages of 10 and 11 for every 0.25SD taller the patient was there was an associated 6% increase in the risk of losing ambulation during follow up.

**Conclusions**

Although RCTs are typically considered the gold standard for estimating treatment efficacy, long-term outcomes in DMD are difficult to capture due to the disease's slow progression. The 18-month EPIDYS trial provides valuable randomised evidence on short-term functional outcomes and is longer than

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| | | comparable studies in DMD. However, using these data to inform long-term outcomes like LOA or respiratory decline requires surrogate relationships, which remain limited and variable in the literature.<br><br>Only one study, Mazzone et al. (2013), provides sufficient data to estimate the probability of LOA based on 10MWT; however, this analysis is limited to a two-year follow-up and applies a threshold that may not be sensitive enough to support long-term extrapolation.[8] The published studies do confirm that the outcomes observed in EPIDYS are clinically meaningful.<br><br>Due to insufficient data to robustly model surrogate relationships from the EPIDYS study, the model adopts a more robust approach using the UK real-world data[2,3] as the external control arm. This approach is aligned with that taken in the ataluren NICE submission[19]. An additional advantage of this approach is that it allows for the use of the Project HERCULES CEM which is driven by endpoints extensively validated by clinicians and patient representatives and aligns with the model structure accepted by NICE in the vamorolone appraisal in DMD (NICE TA1031).[20]<br><br>As discussed in response to Key Issue 4, this approach is further justified by the comparability of the UK real-world data to the givinostat dataset and the consistencies observed in the literature between placebo arms of clinical trials and UK real-world data in DMD.<br><br>Therefore, while the EPIDYS RCT provides strong short-term efficacy signals, its limited follow-up precludes its use for long-term modelling. The use of long-term givinostat data combined with a UK real-world external control arm offers a more reliable and evidence-based approach to estimating long-term comparative effectiveness. |
| 6. Use of 1.5% discounting | Yes | The EAG presents an inconsistent description of the application of the 1.5% discount rate (e.g. page 13 of the EAR) which may be interpreted as the Company applying a 1.5% discount rate to health outcomes across the model time horizon. To clarify, in the base case, the 1.5% discount rate has been applied from year 30 onwards, in accordance with guidance from the HM Treasury Green Book.<br><br>The justification for using the 1.5% discount rate has been discussed in detail in Section B.3.2.2 of the CS and in the response to CQ B23. Rather than repeating those points, we provide further evidence supporting the appropriateness of applying the 1.5% discount rate beyond 30 years. We also note that this approach may be conservative and that applying a 1.5% discount rate across the full time horizon for health outcomes could be more relevant in the context of givinostat.<br><br>The EAG raises several concerns, including that applying the 1.5% rate beyond 30 years deviates from NICE's reference case; that previous DMD appraisals (e.g. vamorolone and ataluren) used a 3.5% rate across the full time horizon; that existing published DMD models also adopt the 3.5% rate; and that |

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| | | there is currently no long-term evidence of benefit for givinostat from RCTs or cohort studies. They also highlight that the long-term benefit of givinostat, particularly post-discontinuation, remains uncertain.<br><br>As detailed in our response to CQ B23, givinostat meets two of the three criteria for applying non-reference discounting, as outlined in the NICE Methods Manual.[21] Specifically, it is indicated for a condition that severely impairs quality of life, and is expected to deliver sustained benefits. These criteria support the assumption of a 1.5% discount rate for health outcomes beyond 30 years and provide support that the 1.5% discount rate may be appropriate across the model time horizon.<br><br>NICE has accepted non-reference discounting in prior evaluations where long-term benefit and disease severity justified deviation from the standard 3.5% rate:<br><br>1. **Onasemnogene abeparvovec (Zolgensma®) for SMA (HST15, 2021)**[22]<br>NICE accepted a 1.5% discount rate for health outcomes, acknowledging the life-threatening nature of SMA and the potential for long-term benefit, despite uncertainties in durability.<br>2. **Strimvelis® for ADA-SCID (HST7, 2018)**[23]<br>The 1.5% rate was accepted due to the potential for sustained benefit. While the committee acknowledged some uncertainty around whether the criteria were fully met, it concluded that both discount rates should be considered during decision-making.<br>3. **Dinutuximab beta for high-risk neuroblastoma (TA538, 2018)**[24]<br>NICE accepted the 1.5% discount rate, based on the potential for cure in a subset of patients for both costs and outcomes.<br><br>As noted in our response to CQ B23, vamorolone met only one of the non-reference discounting criteria, and ataluren was routed through the HST process under a previous version of the NICE Manual, when non-reference discounting criteria had not yet been formally introduced. Thus, comparisons to these appraisals are not directly applicable.<br><br>The EAG references published models in DMD using a 3.5% discount rate, yet it also acknowledges that these are hypothetical models. These models were not designed to assess non-reference discounting under current NICE guidance, and should not be interpreted as precedent that precludes a 1.5% discount rate in the case of givinostat.<br><br>While it is true that no RCT or cohort study extends over the full duration of expected benefits for givinostat, it is incorrect to conclude that there is no evidence of long-term benefit.<br><br>As outlined in the CS, we have robust evidence from both the 18-month randomised EPIDYS trial and its OLE, together comprising one of the longest clinical follow-up periods for any investigational therapy in DMD. This randomised period is longer than the studies underpinning both the ataluren and vamorolone NICE submissions.[19,20] The mean duration of follow-up from the OLE was 1,204.2 days (SD |

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| | | ±446.3; median 1,179.0 [range 99 to 2,259] days). Importantly, givinostat has demonstrated consistent benefit across early TFT endpoints in EPIDYS, and these benefits are shown to translate into long-term outcomes in the OLE. Feedback from UK clinical experts highlights that the delay in LOA observed for givinostat in the OLE, will then have an impact on the overall progression of the disease in the non-ambulatory health states.<br><br>It is also important to acknowledge the realities of trial design in DMD. Clinically meaningful long-term outcomes, e.g. LOA, may not occur until many years after treatment initiation. In UK clinical practice, the typical time from age six (the approved starting age for givinostat per the SmPC) to LOA is approximately six years. Conducting a placebo-controlled RCT over such a period would be unethical and infeasible. These challenges become more relevant when exploring outcomes beyond LOA.<br><br>In addition to the evidence already provided, it is important to recognise that treatment for boys with DMD typically begins at an early stage. However, the most meaningful clinical and patient outcomes take several years or even decades to fully materialise. While the EPIDYS trial demonstrates the clinical benefits of givinostat, the outcomes that are most significant to patients, and which drive costs in the economic model, become apparent over the patient's lifetime. Consequently, the full value of givinostat becomes apparent only many years after treatment initiation.<br><br>**Despite this delay, these long-term outcomes are important to both patients and caregivers today. Therefore, we believe that, in addition to meeting two of the three criteria for non-reference discounting, the 1.5% discount rate is contextually appropriate for givinostat. This rate accurately reflects the long-term nature of the therapy's benefits, while ensuring that its value is appropriately recognised.** |
| 7. Overestimation of caregiver utility impact | Yes – BOI report | As discussed during our factual accuracy check and the TE call on 2nd April 2025, one of our key concerns is that our approach to modelling caregiver QALYs has only been partially explained in the EAR. This partial explanation raises the risk of misinterpretation, particularly when comparing our methodology with that of the EAG. During the TE call, the EAG acknowledged that, due to time constraints, they were unable to fully describe the Company's base case approach to modelling caregiver QALYs, instead focusing on detailing their own approach. Unfortunately, this is not made clear in the EAR, and as a result, there is a risk that a reader may draw incorrect conclusions from the way the Company's approach is presented.<br><br>For example, Table 28 of the EAR states that the utility decrements shown reflect burden of illness (BOI) values used in the Company's economic model. This is incorrect – the values presented are not BOI figures but are instead utility decrements derived from the UK vignette time trade off (TTO) study. In addition, the EAR (page 95) states that the Company applies a bereavement disutility. This statement is |

misleading. A bereavement disutility is typically applied in each model cycle to the proportion of patients who have died, across the entire time horizon. However, as outlined in Section B.3.4.6 of the CS and in response to CQ B14, we have applied a utility decrement to the incremental time spent in the death health state. Since givinostat reduces time spent in this state, it results in negative incremental time in the death state. When this is multiplied by the utility decrement, it yields a positive utility gain for caregivers. This is more accurately described as a utility benefit from extended survival with givinostat, rather than a bereavement disutility, and should not be misrepresented as such.

In our response, we have structured the discussion around three key areas: methodology, data sources, and the number of caregivers. The only new evidence submitted at this stage is the BOI report from Project HERCULES, which has been shared with NICE and clarifies the source of caregiver HRQoL data used in both the vamorolone NICE submission and the EAG's base case.[20,25] This is addressed in the relevant section below. While no further additional evidence is provided, we have included a comparison of the Company's base case and the EAG's approach within each section to help prevent any potential misinterpretation.

**Methodology**

Table L compares the methodological approaches in the Company's base case and the EAG's base case.

**Table L: A comparison of methodological approaches to modelling caregiver QALYs**

| | Company base case approach | EAG approach |
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| **Approach** | Increments relative to midway health state | Disutility |
| **Summary** | Utility increments or decrements are applied to the incremental patient LYs across all health states (including the death health state). This gives the incremental caregiver QALYs. | Utility decrements are applied to the total patient LYs across living patient health states in the givinostat and ECM arms. The incremental caregiver QALYs are then calculated by the difference between the givinostat and ECM arms. |
| **Justification** | The approach reflects the impact of givinostat on caregiver QALYs:<br>• Extended duration in the milder health states are | The approach:<br>• Page 20, EAR: "anchors at the early ambulatory health state and represents progressively worsening |

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| | | | | reflected by additional caregiver QALYs.<br>• Extended duration in the more severe health states are reflected by less caregiver QALYs.<br>• Modest impacts across the patient health states. The extended duration for which the patient is alive is reflected by additional QALYs. | quality of life in subsequent health states."<br>• Page 20, EAR: "has the added benefit of being directly compatible with utility values used in other appraisals of DMD"<br>• Page 95, EAR: "quality of life is accounted for on both ECM and givinostat arms, as otherwise an imbalance is created"<br>• Page 95, EAR: Does "not include the utility decrement for dead patients, otherwise referred to as the bereavement disutility" | |
| | | | **EAG critique** | • The method results in a faster rate of carers' QALYs accruing over shorter periods of time in comparison to the disutility method.<br>• Imbalance created from only considering caregiver QALYs based on incremental patient LYs.<br>• Insufficient evidence for the "bereavement disutility" | NA | |
| | | | **Company critique** | NA | The approach has no face validity. Givinostat is shown to accrue fewer caregiver QALYs across all living health states, except for health state 8 (the most severe health state) for which there is shown to be a benefit to the caregiver. This | |

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| | | results in an overall caregiver detriment applied to givinostat. |

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, Evidence Assessment Group; EAR, Evidence Assessment Report; ECM, established clinical management; NA, not applicable; QALY, quality adjusted life year.

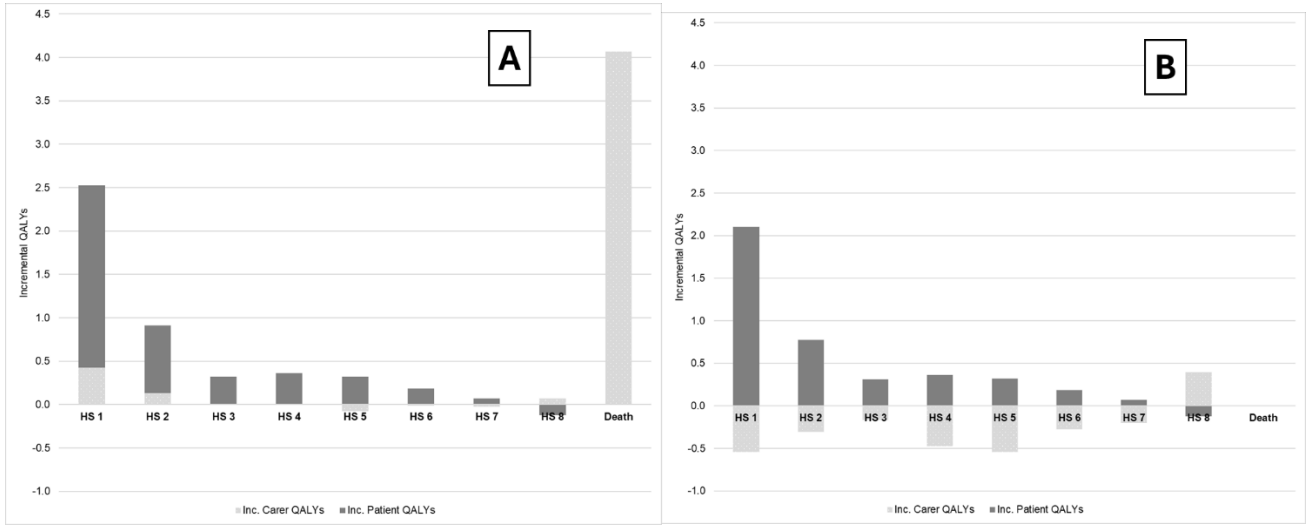
Figure E illustrates the comparison of incremental (discounted) patient QALYs and caregiver QALYs derived from the Company's and EAG's base case approaches. Please note that utility decrements associated with AEs and spinal fusion surgery are excluded from the patient QALYs presented in these diagrams. To ensure a fair methodological comparison, both approaches assume the same utility source (the UK TTO vignetter study) and a single caregiver.

In the Company's approach, modest caregiver QALY gains are observed alongside increases in patient QALYs in health states 1 to 3 (with gains in health state 3 being negligible). No change in caregiver QALYs is seen in health state 4, as it serves as the anchor state. For health states 5 to 7, slight losses in caregiver QALYs accompany the increased patient QALYs, while a small gain in caregiver QALYs is observed in health state 8 due to reduced time spent in this state. The primary driver of caregiver QALY gains is the improvement in patient survival associated with givinostat, which is captured as a positive QALY benefit from reduced time spent in the death health state.

In contrast, the EAG's approach shows caregiver QALY losses for all health states where patient QALYs increase, and a corresponding gain in health state 8 when patient QALYs decrease. Notably, the EAG's method does not directly capture the impact of improved survival with givinostat, although there is an indirect effect through changes in time spent across health states.

As discussed in Table L, we believe the Company's approach better reflects the real-world experience of caregivers over time, aligning with face validity – particularly in recognising the positive impact on caregivers from extended patient survival (i.e. time avoided in the death health state). In contrast, we find it lacks face validity to suggest that improved patient outcomes with givinostat would result in decreased caregiver QALYs. For this reason, our base case continues to assume caregiver utility increments relative to the midpoint health state.

**Figure E: Comparison of the incremental (discounted) QALYs accrued by patients and caregivers across the Company's base case (A) and the EAG's base case (B)**




Abbreviations: EAG, Evidence Assessment Group; QALY, quality adjusted life year.

## Data source

Table M provides a comparison of the data sources used in the Company's base case and the EAG's base case. As outlined in Table M, there has been some confusion and misrepresentation regarding the utility values reported in TA1031 which inform the EAG's base case. Although these values were reported by caregivers, they were intended as proxy assessments of patient HRQoL – not direct measures of caregiver HRQoL. The full BOI report, which provides more detail on these data, has been shared with NICE and the EAG following the TE call to support clarification.

While caregiver HRQoL was assessed in the BOI study using the CarerQoL instrument, it did not generate utility values. As a result, the use of these data as utility inputs reflecting caregiver HRQoL is not appropriate. Therefore, our base case continues to use the utility values derived from the UK caregiver vignette study. As detailed in Section B.3.4.3 of the CS, this is a well-conducted study with 200 respondents, the values have face validity across the health states, and the health states align with the economic model.

**Table M: A comparison of data sources informing caregiver utilities**

| | Company base case approach | EAG approach |
|---|---|---|
| **Source** | UK vignette TTO study | BOI study from TA1031. Note in the TE call, it was highlighted that these values are inappropriate – as discussed below. |
| **Justification** | The data source:<br>• Well-conducted and robust study with N=200 respondents<br>• Aligns with the health states in the model<br>• Face validity of worsening utilities across progression of health states<br>• TTO methodology may be more sensitive to the challenges faced by caregivers of people with DMD | • Page 20, EAR: "The EAG prefer utility decrements relative to the early ambulatory health state from the BOI study, which were also preferred in TA1031, the appraisal for vamorolone" |
| **EAG critique** | • Not comparable with previous NICE appraisals.<br>• The EAG notes while any vignette study maybe accepted as a source of utilities, the NICE methods guide stipulates evidence should be derived from a synthesis of peer-reviewed literature to make the case for the inappropriate use of EQ-5D | NA |
| **Company critique** | NA | As discussed during the TE call, there has been some confusion |

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| | | | | regarding the BOI values referenced from TA1031. The utility values presented in TA1031 were reported by caregivers but were intended as proxy assessments of patient HRQoL, not as direct measures of caregiver HRQoL. The full BOI report has since been provided to NICE and the EAG following the TE call.<br>While caregiver HRQoL was assessed in the study using the CarerQoL instrument, no utility data were derived from this measure. As such, these values are not appropriate for use in modelling caregiver utilities |

Abbreviations: BOI, burden of illness; EAG, Evidence Assessment Group; EAR, Evidence Assessment Report; ECM, established clinical management; HRQoL, health-related quality of life; NA, not applicable; QALY, quality adjusted life year; TE, technical engagement; TTO, time trade off.

**Number of caregivers**

Table N compares the Company approach to number of caregivers with the EAG's approach. Based on clinical expert feedback received during the committee meetings of the vamorolone NICE appraisal, it was emphasised how the impact of diagnosis and progression of DMD impacts the whole family network (e.g. siblings and grandparents) as well as requiring additional support from outside this network (e.g. schools). Therefore, we consider that the base case of two caregivers is conservative.

**Table N: A comparison of number of caregivers assumed in the caregiver QALYs calculations**

| | Company base case approach | EAG approach |
|---|---|---|
| **Number of caregivers** | Average of two across all health states | One caregiver in ambulatory health states, increasing to two for non-ambulatory health states |
| **Justification** | • Aligning with feedback from clinical experts in the vamorolone NICE submission | • Page 96, EAR: "The EAG prefers modelling an increasing caregiver burden as in the vamorolone appraisal in TA1031, the number of carers on the were assumed to be 1 for ambulatory health states (1-3), and 2 caregivers for non-ambulatory health states" |
| **EAG critique** | Not comparable with previous NICE appraisals | NA |
| **Company critique** | NA | The assumption of two caregivers may be conservative as feedback from patient advocacy groups heard during the second committee meeting for vamorolone emphasised how the impact of diagnosis and progression of DMD impacts the whole family network (e.g. siblings and grandparents) as well as requiring additional support from outside this network (e.g. schools) |

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, Evidence Assessment Group; EAR, Evidence Assessment Report; ECM, established clinical management; NA, not applicable; QALY, quality adjusted life year.

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| 8. Costs and quality of life assumed the same in the full ventilation states and night ventilation states | No | The Company acknowledged the limitations of the data informing base case costs and utilities for the full and night-time ventilation health states, as detailed in CQ B17. In response, an alternative scenario analysis was presented to explore this uncertainty. This was limited to a scenario analysis to avoid additional uncertainty from incorporating data from multiple sources within the base case. Additionally, cost estimates from Morgan et al. (2024) represent an average across both night-time and full ventilation health states.[26] Therefore, applying a multiplier to these estimates leads to an overestimation of total costs for patients with DMD.<br><br>As noted in the EAR (page 22), the EAG preferred using costs and utilities from the BOI study in the base case. This preference is based on the alignment between the BOI health state definitions and those used in the Company's model, including separate estimates for health states 7 and 8.<br><br>In the EAG's base case, costs were sourced from the vamorolone NICE submission, which references the BOI study and applies a 0.57 multiplier. However, the derivation of this multiplier is unclear, and we do not have access to the calculations used in the vamorolone NICE submission to assess their validity. Concerns remain regarding the robustness of the BOI study as a data source for the base case. As detailed in Section B.3.5.1 of the CS, BOI cost estimates are based on physician- and patient-reported data from a small number of respondents per health state (ranging from 2 to 15), resulting in large standard errors. While these estimates are aligned with health state definitions, the data are highly uncertain.<br><br>In contrast, the Morgan et al. (2024) cost data (used in the Company's base case) are derived from much larger patient samples: 387 in the ambulatory state, 188 in the non-ambulatory non-ventilated state, and 64 in the non-ambulatory ventilated state.[26]<br><br>Similarly, in the EAG's base case, utility values were also taken from the BOI study. These data are limited, with 0 to 8 responses per health state. In cases where no data were available, utility values defaulted to those from Landfeldt et al. (2017), introducing additional uncertainty through reliance on multiple sources. Furthermore, the BOI utility values are based on the DMDQoL, which is not aligned with NICE's preferred measure, the EQ-5D. In contrast, utility data used in the Company's preferred base case were sourced from Audhya et al. (2023), which used EQ-5D and included response counts ranging from 8 to 23 across health states.[27]<br><br>In response to Key Issue 7, the full BOI report has been shared with NICE and the EAG to provide greater transparency regarding these limitations.<br><br>**Despite the different approaches used to address data limitations, both the Company's and EAG's scenario analyses result in lower ICERs than the base case. Notably, the EAG's scenario** |

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| | | **results in a greater reduction in the ICER than the Company's. This suggests that the base case ICER may be conservative.** |
| 9. Overestimation by NHM of survival and DMD clinical progression events | No | In Key Issue 9, the EAG highlights that the updated NHM underestimates survival compared to clinical opinion at ages 15, 20, 25, 30, and 35, with alignment only observed at ages 40 and 50 (as shown in Table 24 of the EAR, replicated from Tables 45 and 46 of the CS).<br>While it is correct that the updated NHM predicts lower survival than clinical opinion for ages 15–35, the survival estimates remain within the range observed across all available data sources. It is also important to note that the clinical feedback was based on input from six clinicians, which introduces some degree of uncertainty. Therefore, we consider that the survival projections from the updated NHM are consistent with the available evidence.<br>The EAG has suggested that further cohort studies reporting both survival and DMD milestones would help to resolve this issue. We agree with this recommendation. However, in the absence of such data, we believe the NHM provides a reasonable and evidence-aligned prediction of survival, supported by both existing data and clinical expert opinion. |
| 10. Mismatch of HERCULES NHM and available RCT data on givinostat | No | In Key Issue 10, the EAG raised concerns about the model structure used in the Company's base case relative to the randomised evidence from the EPIDYS clinical trial for givinostat. While the EAG acknowledges that the Project HERCULES model, which forms the basis of the Company's base case, provides a strong conceptual framework for DMD, they suggest that integrating the available data from the EPIDYS trial into the Project HERCULES model would be an improvement. The EAG also notes that the Project HERCULES model structure has been accepted in previous appraisals.<br>In response to Key Issue 5, we have highlighted that while the EPIDYS trial offers strong signals for short-term efficacy, its limited follow-up restricts its utility for long-term modelling. Therefore, the model instead takes a more robust approach by using UK real-world data as the external control arm. This aligns with the approach taken in the ataluren NICE appraisal.[19] The combination of long-term givinostat data with a UK real-world external control arm provides a more reliable and evidence-based approach for estimating long-term comparative effectiveness. |
| 11. Implementation of treatment effect within the economic model | No | As outlined by the EAG in Key Issue 11 of the EAR, data on age at NIV and age FVC <1L are not available for givinostat; these endpoints have not yet been reached within the clinical trial follow-up. Therefore, these timepoints are estimated by applying acceleration factors - derived from the UK registry study - to the age at LOA. As a result, both age at NIV and age at FVC <1L are dependent on age at LOA and the associated acceleration factor. |

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| | | This means that applying hazard ratios for all three endpoints (LOA, NIV, and FVC <1L) directly to transition probabilities in the economic model would lead to an overestimation of the benefit of givinostat. Additionally, the model includes more granular health state transitions than these endpoints. For example, three states within the ambulatory phase, which means age at LOA encompasses transitions from health state 1 to 2, 2 to 3, and 3 to 4. Applying hazard ratios based on age at LOA for each of these more granular transitions would further overestimate the benefit of givinostat.<br><br>To avoid issues associated with overestimating the benefit of givinostat, the EAG has suggested applying the hazard ratio for age at LOA only within the economic model. This is only applied to the transition from health state 2 to 3.<br><br>From the Company's perspective, the EAG's approach underestimates the value of givinostat within the ambulatory health states - specifically in slowing disease progression between health states (e.g., from health state 1 to 2 and from 3 to 4) - as well as its effect on long-term clinical outcomes. Table O illustrates this by comparing the median ages at key disease milestones under the Company's base case and the EAG's preferred modelling approach. For the purposes of isolating the methodological differences in the economic models, both approaches use the same source of relative efficacy data i.e., the UK registry data. In the EAG's approach, a HR of 0.185 is applied to the transition from health state 2 to 3.<br><br>As shown in Table O, under the EAG's approach, no treatment benefit is assumed for the transition from health state 1 to 2. As a result, the median age at the milestone "unable to stand from supine" is identical for patients treated with givinostat and those treated with ECM. This is inconsistent with the treatment effect of givinostat on age at LOA.<br><br>To estimate the timing of longer-term disease milestones for patients treated with givinostat, the Company uses acceleration factors derived from the UK registry. Specifically:<br>• The ratio of median age at NIV to median age at LOA for ECM is 1.50 (18.46 / 12.28), which is applied as the acceleration factor to derive median age at NIV for givinostat based on its estimated LOA.<br>• Similarly, the ratio for FVC <1L to LOA is 1.94 (23.86 / 12.28), and is used to estimate median age at FVC <1L for givinostat.<br><br>In the Company's base case, the resulting ratios for givinostat are consistent with these UK registry-based acceleration factors:<br>• NIV: 1.50 = 26.9 / 17.9<br>• FVC <1L: 1.94 = 34.7 / 17.9 |

This indicates that the effect of delaying LOA with givinostat is proportionally carried through to later-stage outcomes, in line with the real-world data observed for ECM.

Conversely, in the EAG's approach, the corresponding ratios for givinostat are significantly lower:

- NIV: 1.22 = 23.8/19.4
- FVC <1L: 1.45 = 28.1/19.4

This implies that, within the EAG's modelling framework, the delay in LOA for givinostat has a disproportionately smaller impact on long-term outcomes compared to ECM.

**Table O: Comparison of key milestones for ECM and givinostat under the Company and the EAG's preferred methodological approach**

| Median age at: | ECM | Givinostat | EAG |
|---|---|---|---|
| Unable to stand from supine | 8.7 | 11.3 | 8.7 |
| Loss of ambulation | 12.1 | 17.9 | 19.4 |
| Loss of HTMF | 15.8 | 26.0 | 23.7 |
| Starting ventilation | 16.0 | 26.9 | 23.8 |
| Starting full-time ventilation | 20.3 | 34.8 | 28.1 |
| Death | 25.4 | 39.3 | 33.7 |

Abbreviations: EAG, Evidence Assessment Group; ECM, established clinical management;.

As outlined in Section B.3.3.2 of the CS and in response to CQ B5 and B20, the Company acknowledges that directly applying HRs from the ITCs to the model would overestimate the benefit of givinostat. This is consistent with the EAG's critique in Key Issue 11 and is why HRs are not applied directly in the model.

Instead, the Company uses a SOLVER-based approach to estimate the HRs required to align the modelled median outcomes with those observed in the ITCs. This approach was discussed during the TE call, where it was acknowledged that the Company does not apply ITC-derived HRs directly. It was further clarified that the EAG's concern regarding potential "double counting" of treatment effect pertained to the scenarios conducted by the EAG, not the approach adopted by the Company.

Therefore, the Company considers its method of incorporating ITC data to be appropriate, avoiding double counting while enabling the generation of externally valid estimates of outcomes for givinostat.

## Additional issues

**All:** Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

**Table 3 Additional issues from the EAR**

| Issue from the EAR | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|
| **Additional issue 1:** Givinostat monitoring costs | Page 97, EAR | No | In the EAR, it is noted that clinical advice provided to the EAG indicated that monitoring costs related to givinostat would be relevant to NHS clinical practice. In response to CQ B8, we agreed with this assessment and referenced the SmPC for givinostat, which recommends regular monitoring of platelet counts and triglycerides to guide dosage adjustments. In our response, we included a scenario analysis based on non-consultant led monitoring. However, in the EAG's preferred base case, consultant-led monitoring costs are assumed. Based on feedback from clinicians throughout the NICE process, we anticipate that monitoring in clinical practice may involve a combination of non-consultant and consultant-led care. Nevertheless, we are prepared to proceed with the conservative assumption of consultant-led monitoring for givinostat, and these costs will be reflected in the updated cost-effectiveness results. |
| **Additional issue 2:** Givinostat hydrochloride versus givinostat free base case | Follow-up email from NICE (22nd April 2025)<br>• In the "Cost data" tab of the model Cells H48:56, mg refer to | No | The Company submitted the EPIDYS dosing to both the EMA and the Food and Drug Administration (FDA). Givinostat received approval in the US for the treatment of patients with DMD on 21 March 2024, during the Day 120 clock stop for the Marketing Authorisation Application (MAA).<br>During the New Drug Application (NDA) review, the FDA raised concerns about the complexity of the dose/regimen dose instructions and about patients' exposures and dose related AEs (mainly thrombocytopaenia, hypertriglyceridaemia, gastrointestinal symptoms). In addition, the FDA noted that the pharmacometrics analyses presented in the NDA showed higher exposure in patients in the 60 to 70Kg weight band compared to lighter patients when receiving the same |

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| | givinostat hydrochloride (10 mg/ml) derived from the "Givinostat Dose calculation" tab. Whereas the mg/ml in Cell I48 refers to the free base (8.86 mg/ml)<br>• The per cycle costs in Column O combine mg of givinostat hydrochloride with the price per mg of the free base.<br>Please could you look into this possible error and correct if needed | | dose level. This led to an Information request requesting the Company to conduct pharmacometrics simulations (PK, PK-PD) to evaluate a potential alternative dosing regimen, with a reduced number of weight bands, to be compared with the originally proposed dose regimen applied in EPIDYS.<br>In response to the request, the Company conducted the requested analysis evaluating the simplified dosing regimen that still achieves exposures equivalent to those observed in EPIDYS and further optimised the FDA revised dosing regimen, to decrease the likelihood of dose reductions due to platelet count reductions in the heavier weight bands (>40 kg). During the final stages of labelling discussions, the FDA proposed additional minor revisions to the initial dose reduction, to further reduce the risk of platelet count reductions in heavier patients. These analyses and discussions with the FDA led to the dose regimen now included in the givinostat USPI & UKPI. The revised dose regimen represents a simplification of the dosing instructions, leading to the use of only one oral syringe for the administration, and also addressing the FDA's concerns regarding the complexity of dosing.<br>In the economic model, dosing is derived from the volume (in mL) used in the EPIDYS clinical trial, and the corresponding dose in milligrams was calculated based on the 10 mg/mL concentration. As the NICE Team have highlighted, this approach is inconsistent with the commercially available 8.86 mg/mL formulation used to inform drug costs in the model. As a result, there is a mismatch between the calculated dose (mg) and the cost inputs. We have corrected this error as part of the changes to the cost-effectiveness results in this technical engagement response.<br>Table P presents the corrected Dose A, Dose B, and Dose C values from EPIDYS, updated using the 8.86 mg/mL concentration – these values replace the information on mg dosing from EPIDYS in Section B.2.3.1 and Appendix M.2 of the CS.<br>The correct text from Section B.2.3.1 should state, the initial doses of givinostat were based on a dose ranging evaluation in a mouse model,[28] in addition to the results of the previous Phase 2 study in boys with DMD[29] and several studies of other disorders.[30,31] A flexible treatment regimen was used, in which a fixed starting dose of givinostat was given to maximise efficacy but dose reductions were prespecified if AEs occurred, such as platelet count reduction or diarrhoea.[30,31] The weight-based starting dose was initially **2–7 mL (17.72–62.02 mg)** oral givinostat twice a day, with a reduced dose of **1.3–4.7 mL (11.52–41.64 mg)** twice a day (see **Table P**, **Dose A and B in the "Givinostat Dose Calculation" sheet**). A protocol amendment following the masked safety review (in June 2018), reduced the starting dose to Regimen 2 (**Table P**) for boys who were recruited after the amendment. The starting dose for Regimen 2 |

was **1.3–4.7 mL (11.52–41.64 mg)** twice a day, with a reduced dose of **1.1–3.7 mL (9.75–32.78 mg)** twice a day (**Table P, Dose B and C in the "Givinostat Dose Calculation" sheet**). A subsequent protocol amendment, applying only to France, moved all boys to Regimen 2.[30,31] If boys gained weight during the study, the drug dose was kept unchanged; if boys lost weight the dose was adjusted as described in the CS.

These revised values have been incorporated into the cost-effectiveness model in the "Givinostat Dose Calculation" sheet. Table Q provides an update of Table 42 from the CS. This correction reduces the original base case ICER by 11.0%.

### Table P: Dose calculations informing the economic model

| Weight | 10-12,5 Kg | 12.5-20 Kg | 20-25 Kg | 25-30 Kg | 30-40 Kg | 40-50 Kg | 50-60 Kg | 60-70 Kg | 70 Kg |
|---|---|---|---|---|---|---|---|---|---|
| **Dose A** | | | | | | | | | |
| Oral suspension (mL) | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 | 5.0 | 5.5 | 6.0 | 7.0 |
| Dose per day ml (A) | 4.0 | 5.0 | 6.0 | 7.0 | 8.0 | 10.0 | 11.0 | 12.0 | 14.0 |
| Dose per day mg (A) | 35.4 | 44.3 | 53.2 | 62.0 | 70.9 | 88.6 | 97.5 | 106.3 | 124.0 |
| **Dose B** | | | | | | | | | |
| Oral suspension (mL) | 1.3 | 1.7 | 2.0 | 2.3 | 2.7 | 3.3 | 3.7 | 4.0 | 4.7 |
| Dose per day ml (B) | 2.6 | 3.4 | 4.0 | 4.6 | 5.4 | 6.6 | 7.4 | 8.0 | 9.4 |
| Dose per day mg (B) | 23.0 | 30.1 | 35.4 | 40.8 | 47.8 | 58.5 | 65.6 | 70.9 | 83.3 |
| **Dose C** | | | | | | | | | |
| Oral suspension (mL) | 1.1 | 1.3 | 1.6 | 1.9 | 2.1 | 2.7 | 2.9 | 3.2 | 3.7 |
| Dose per day ml (C) | 2.2 | 2.6 | 3.2 | 3.8 | 4.2 | 5.4 | 5.8 | 6.4 | 7.4 |
| Dose per day mg (C) | 19.5 | 23.0 | 28.4 | 33.7 | 37.2 | 47.8 | 51.4 | 56.7 | 65.6 |

Abbreviations: kg, kilogram; mg, milligram; N, number

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Table Q: Number of patients receiving each of the weight-based dose distributions in the EPIDYS clinical trial and calculation of average weight-based dose distribution (updated Table 42 from CS)
<table>
<tr><th>Weight</th><th>10-12.5 Kg</th><th>12.5-20 Kg</th><th>20-25 Kg</th><th>25-30 Kg</th><th>30-40 Kg</th><th>40-50 Kg</th><th>50-60 Kg</th><th>60-70 Kg</th><th>70 Kg</th></tr>
<tr><td>Dose Regimen 1 starting dose, N (%)</td><td>0 (0.0%)</td><td>7 (70.0%)</td><td>15 (79.0%)</td><td>18 (58.1%)</td><td>6 (15.0%)</td><td>1 (6.7%)</td><td>0 (0.0%)</td><td>0 (0.0%)</td><td>0 (0.0%)</td></tr>
<tr><td>Dose Regimen 1 permitted dose reduction, N (%)</td><td>0 (100.0%</td><td>1 (10.0%)</td><td>2 (10.5%)</td><td>10 (32.3%)</td><td>23 (57.5%)</td><td>10 (66.7%)</td><td>1 (100.0%)</td><td>2 (100.0%)</td><td>0 (100.0%</td></tr>
<tr><td>Dose Regimen 2, N (%)</td><td>0 (0.0%)</td><td>2 (20.0%)</td><td>2 (10.5%)</td><td>3 (9.7%)</td><td>11 (27.5%)</td><td>4 (26.7%)</td><td>0 (0.0%)</td><td>0 (0.0%)</td><td>0 (0.0%)</td></tr>
<tr><td>Average dose per day (mg)</td><td>23.0</td><td>38.6</td><td>48.7</td><td>52.4</td><td>48.4</td><td>57.6</td><td>65.6</td><td>70.9</td><td>83.3</td></tr>
</table>
Abbreviations: kg, kilogram; mg, milligram; N, number
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<td>Additional issue 3: Differences between trial and SmPC dosing</td>
<td>Follow-up email from NICE (22nd April 2025)<br>• The dosing regimens used in the trial are slightly different to those in the SmPC (Tables 1 & 2)<br>• Please could you comment on any impact this might have on the estimates of</td>
<td>No</td>
<td>The economic model applies the givinostat dosing regimen observed in the EPIDYS trial to ensure alignment with the source of efficacy data.<br><br>The SmPC provides updated dosing guidance informed by the outcomes of the EPIDYS trial. The dosing evolution for givinostat reflects a balance between maximising efficacy and managing safety. As no new safety concerns emerged during EPIDYS, the SmPC recommends slightly higher dosing than was used in the trial. As higher dosing may be associated with improved outcomes, it is reasonable to expect potential gains in effectiveness. However, to maintain consistency with the efficacy data that informs the economic model, the dosing used in EPIDYS is assumed to be representative of the dose linked to those outcomes.<br><br>However, unlike the fixed dosing in EPIDYS, the model incorporates dose adjustments based on patient weight over time. Weight data for boys aged 6–18 years are derived from growth charts published by the Royal College of Paediatrics and Child Health.[32] This approach may represent a conservative assumption, as it is possible that if dosing in EPIDYS had been adjusted for weight, additional gains in effectiveness could have been observed.</td>
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| | cost-effectiveness | | |
| **Additional issue 4:** Wastage | Follow-up email from NICE (22nd April 2025)<br>• Current drug costs appear to be applied as a per cycle cost (i.e per mg), after compliance/RDI and ignoring wastage (i.e if someone discontinues part way through a bottle).<br>• 3.5.6 of PMG24 states wastage should be taken into account.<br>• Please could you comment on this and on any impact this might have on estimates of cost-effectiveness as well as | No | Givinostat, as described in the SmPC and clinical practice, is formulated as an oral suspension supplied in bottles, each containing a defined amount of active ingredient. Dosing can be tailored to the individual, with the flexibility to use full or partial bottles as needed. Unopened bottles have a shelf life of three years, and once opened, the product remains usable for up to 60 days. In the event of a dose reduction, the remaining medication is not wasted but retained for future use, with clinicians simply delaying the next reorder. This flexible dosing approach differs from drugs provided in fixed-dose vials or pre-filled syringes, where unused portions are often discarded. As a result, drug wastage is expected to be negligible, with doses prepared to match individual patient requirements. |

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| | provide scenarios that could model/emulate wastage (e.g applying a fraction of the cost of a bottle at discontinuation) | | |
| **Additional issue 5:** Face validity of time on treatment | Follow-up email from NICE (22nd April 2025)<br>• Is there a plausible reason why discontinuation would be greater for givinostat + steroids (a more effective treatment) than steroids alone?<br>• Please could you comment on this | No | For clarity, in the economic model the discontinuation rate for steroids is assumed to be equal in both treatment arms. This is described in Section B.3.2.3 and Section B.3.3.4 of the CS, it is assumed that givinostat will not impact the CS use.<br>Nevertheless, the discontinuation rate for givinostat is modelled as higher than for corticosteroids alone, in line with EPIDYS trial data. Over the 18-month follow-up, 5.9% of patients in the givinostat arm discontinued treatment, compared with 3.3% in the placebo arm. In EPIDYS, givinostat was administered in addition to CS, and it is assumed that NICE's question refers to this combination. While this difference is relatively small, it may reflect the added burden of combination therapy. Although givinostat is generally well tolerated, its use alongside steroids introduces additional side effects that may contribute to a modestly higher discontinuation rate. This may contribute to the observed difference in discontinuation rates. |
| **Additional issue 6:** Model starting age | Follow-up email from NICE (22nd April 2025)<br>• Currently set to 6 years, lowest age in the MA, | No | The economic model begins at age six, consistent with the SmPC for givinostat, which specifies use in boys aged six years and older. This starting age also aligns with the EPIDYS clinical trial, which enrolled boys aged at least 6 years. By modelling from age six, the population reflects the earliest point of trial eligibility and aligns with the intended treatment population in UK clinical practice. |

| | | | |
|---|---|---|---|
| | reflects the incident age<br>• Should the prevalent age be explored? Mean age in the trial was closer to 10 years<br>• Please could you comment on this, which age should be modelled and used for decision making | | In DMD, earlier treatment is known to accrue greater benefits in preserving muscle function and delaying disease progression. Although the mean age in the EPIDYS trial was 9.8 years (Overall ITT population) in the givinostat arm, in UK clinical practice givinostat is expected to be initiated at the earliest opportunity i.e., when boys become eligible at age six. Starting treatment earlier than observed in EPIDYS will likely result in better preservation of mobility and function than observed in the trial population. Therefore, the EPIDYS data used in the model likely underestimates the full potential benefits of givinostat given from age six. |
| **Additional issue 7:** Application of severity modifier | Follow-up email from NICE (22nd April 2025)<br>• Please could you ensure that the severity modifier is only applied to patient incremental QALYs for all estimates of cost-effectiveness presented. | No | This is reflected in our changes to the Company's cost-effectiveness results. |

# Summary of changes to the company's cost-effectiveness estimate(s)

In the revised base case and as part of the TE process, an updated PAS for givinostat has been submitted. A simple PAS of [redacted]% is applied to the cost of givinostat which reduces the cost per 8.86 mg/mL 140 mL bottle from £13,846 to [redacted].

In addition to the updated PAS, a number of changes have been made in response to issues raised in the EAR and throughout TE. Table 4 reflects the changes from the original base case to the revised base case. Table 5 presents the revised base case results with the updated PAS.

**Table 4: Changes to the company's cost-effectiveness estimate**

| Key issue(s) in the EAR that the change relates to | Company's base case before technical engagement | Change(s) made in response to technical engagement | Impact on the company's base-case incremental cost-effectiveness ratio (ICER) |
|---|---|---|---|
| Additional issues, Scenario 7 in EAR | Givinostat monitoring costs: excluded | Givinostat monitoring costs: included as per EAG's base case | Original base case ICER: £141,583. Inclusion of givinostat monitoring costs as per EAG base case: £142,098 (+0.36%) |
| Additional issues, givinostat dosing | Givinostat dosing calculations: based on 10 mg/mL. Not aligned with the bottle size and costing | Givinostat dosing calculations: based on 8.86 mg/mL. Aligned with the bottle size and costing. | Original base case ICER: £141,583. Update to 8.86mg/mL bottle size: £125,999 (-11.01%) |
| Additional issues, severity modifier | Severity modifier: applied to incremental patient and caregiver QALYs | Severity modifier: applied to incremental patient QALYs | Original base case ICER: £141,583. Apply severity modifier to incremental patient QALYs only: £198,503 (+40.20%) |
| Company's base case following technical engagement (or revised base case) | Incremental QALYs: 15.98 | Incremental costs: £2,835,222 (excluding PAS), £[redacted] (including updated PAS) | Revised base-case ICER: £177,377 (+25.28% from original base case ICER; excluding PAS), £[redacted] (including updated PAS) |

**Table 5: Revised base case results (with updated PAS)**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs* | ICER (£/QALY)* |
|---|---|---|---|---|---|
| **Givinostat** | £[redacted] | 19.33 | | | |
| **ECM** | £99,448 | 6.14 | £[redacted] | 15.98 | £[redacted] |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.
*Including the 1.7 severity modifier, applied to incremental patient QALYs only

**Sensitivity analyses around revised base case**

The probabilistic (PSA) and one-way sensitivity analyses (OWSA) have been updated in line with the revised base case and the updated PAS.

Table 6 presents the probabilistic results. The probabilistic ICER is £[redacted]. This is congruent with the deterministic ICER of £[redacted], as demonstrated by the overlap in markers showing the deterministic and probabilistic base case in the cost-effectiveness plane (Figure 1). The CEAC is depicted in Figure 2. The proportion of simulations considered cost-effective at a threshold of £30,000 and £50,000 are 8.1% and 80.8%, respectively.

**Table 6: Probabilistic results (with updated PAS) | Revised base case**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs* | Probabilistic ICER (£/QALY)* | Deterministic ICER (£/QALY)* |
|---|---|---|---|---|---|---|
| **Givinostat** | £[redacted] | 19.64 | | | | |
| **ECM** | £99,086 | 6.17 | £[redacted] | 16.35 | £[redacted] | £[redacted] |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.
*Including the 1.7 severity modifier, applied to incremental patient QALYs only.

**Figure 1: Cost-effectiveness plane | Revised base case | 1,000 iterations (with updated PAS)**



Abbreviations: PAS, patient access scheme; QALY, quality adjusted life year

**Figure 2: Cost-effectiveness acceptability curve | Revised base case | 1,000 iterations (with updated PAS)**



Abbreviations: NMB, net monetary benefit; PAS, patient access scheme

Results for the ten most influential parameters are depicted in a tornado diagram in Figure 3 and detailed in Table 7 using the ICER as the outcome and applying the updated PAS for givinostat. The interpretation through which the parameters impact the cost-effectiveness results remains aligned with that described in the original CS (Section B.3.11.2).

**Figure 3: Tornado diagram | Revised base case | ICER (with updated PAS)**



Abbreviations: HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

**Table 7: One-way sensitivity analysis (with updated PAS) | Revised base case**

| Parameter | ICER at upper value of parameter | ICER at lower value of parameter |
|---|---|---|
| Number of caregivers | £[redacted] | £[redacted] |
| Givinostat HR: To state 2 - Late ambulatory | £[redacted] | £[redacted] |
| Number of patients discontinuing givinostat - OLE | £[redacted] | £[redacted] |
| Givinostat HR: To state 3 - Transfer | £[redacted] | £[redacted] |
| Average weight: Age 18 | £[redacted] | £[redacted] |
| Givinostat number with dose modifications - OLE | £[redacted] | £[redacted] |
| Patient utilities: health state 1 - Early ambulatory | £[redacted] | £[redacted] |
| Givinostat HR: To state 4 - HTMF, no ventilation | £[redacted] | £[redacted] |
| Givinostat HR: To state 7a - No HTMF, night-time ventilation | £[redacted] | £[redacted] |
| Caregiver utilities: health state 1 - Early ambulatory | £[redacted] | £[redacted] |

Abbreviations: HR, hazard ratio; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

Table 8 presents the deterministic scenario analyses for the revised base case with the updated PAS. These results update those presented in Table 95 in the CS. Additionally, in response to Key Issue 8 i.e. “Costs and quality of life assumed the same in the full ventilation states and night ventilation states” two additional scenarios are presented reflecting the Company’s response to exploring this assumption and the EAG’s response to exploring this assumption – both scenarios indicate the base case ICER may be conservative.

**Table 8: Deterministic scenario analyses (with updated PAS) | Revised base case**

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | % change from base-case ICER |
|---|---|---|---|---|
| Base-case | £[redacted] | 16.0 | £[redacted] | 0.0% |
| **Key issue 3:** inclusion of all givinostat patients in the MAICs | £[redacted] | 16.28 | £[redacted] | -1.68% |
| **Key issue 8:** Company approach i.e., multiplier in health state 8 | £[redacted] | 15.98 | £[redacted] | -0.73% |
| **Key issue 8:** EAG approach i.e., BOI source for costs and patient utilities | £[redacted] | 16.55 | £[redacted] | -1.87% |
| Time horizon: 50 years | £[redacted] | 15.0 | £[redacted] | 5.8% |
| Time horizon: 60 years | £[redacted] | 15.7 | £[redacted] | 1.6% |
| Perspective: Societal using Landfeldt et al. | £[redacted] | 16.0 | £[redacted] | 17.2% |
| Perspective: Societal using Project HERCULES BOI | £[redacted] | 16.0 | £[redacted] | 16.6% |
| Discount rates: 3.5% costs and 1.5% outcomes across model time horizon | £[redacted] | 19.7 | £[redacted] | -19.1% |
| Distribution and dosing schedule for CS: UK real-world data | £[redacted] | 16.0 | £[redacted] | 1.2% |
| NHM: Updated analysis 1 | £[redacted] | 20.2 | £[redacted] | -17.1% |
| NHM: Original | £[redacted] | 15.9 | £[redacted] | 4.7% |
| Source for treatment duration, adverse events, compliance, and dose modifications: EPIDYS | £[redacted] | 16.0 | £[redacted] | -9.0% |
| Givinostat continuation rule: until fulltime ventilation | £[redacted] | 16.0 | £[redacted] | -4.5% |
| Givinostat continuation rule: until loss of HTMF | £[redacted] | 16.0 | £[redacted] | -19.0% |
| Givinostat continuation rule: until loss of ambulation | £[redacted] | 16.0 | £[redacted] | -39.9% |
| CS continuation rule: until fulltime ventilation | £[redacted] | 16.0 | £[redacted] | 0.0% |
| CS continuation rule: until loss of HTMF | £[redacted] | 16.0 | £[redacted] | -0.4% |
| CS continuation rule: until loss of ambulation | £[redacted] | 16.0 | £[redacted] | -0.9% |

| | | | | |
|---|---|---|---|---|
| Patient utilities: Landfeldt et al. | £[redacted] | 15.2 | £[redacted] | 4.8% |
| Patient utilities: Project HERCULES BOI | £[redacted] | 16.5 | £[redacted] | -3.4% |
| Number of caregivers: three | £[redacted] | 20.6 | £[redacted] | -22.3% |
| Caregiver utilities: Landfeldt et al. | £[redacted] | 18.8 | £[redacted] | -14.8% |
| Caregiver HRQoL approach: utilities | £[redacted] | 16.0 | £[redacted] | 0.0% |
| Caregiver HRQoL approach: disutilities | £[redacted] | 16.0 | £[redacted] | 0.0% |
| Caregiver HRQoL approach: increments relative to severe | £[redacted] | 16.0 | £[redacted] | 0.0% |
| Health state costs: Landfeldt et al. | £[redacted] | 16.0 | £[redacted] | 6.3% |
| Health state costs: Project HERCULES BOI | £[redacted] | 16.0 | £[redacted] | -0.5% |

Abbreviations: BOI, burden of illness; CS, corticosteroids; ECM, established clinical management; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; NHM, natural history model; OLE, open-label extension; PAS, patient access scheme.

# Appendix

## Selection of evidence to support indirect treatment comparison

The published UK real-world data source, i.e. North Star data from three centres presented by Pietrusz[3,4], is the most appropriate data source when estimating the efficacy of patients receiving ECM, as this reflects both the UK DMD population and UK clinical practice.

This dataset is preferred compared with alternative UK and non-UK datasets due to:

- Timing of data collection (published in 2023/2024)
- Availability of Kaplan-Meier curves for multiple ambulatory and non-ambulatory outcomes, ensuring a consistent dataset can be included across outcomes when conducting the unanchored MAICs

Note that no access to individual patient-level data (IPD) was available for any study for established clinical management (ECM). Appendix Table 1 summarises at a topline level the rationale for selecting the RWE data sources for the ITC. Appendix Table 2 provides more detailed reasons for inclusion or exclusion of each potential source identified by the SLR.

### Appendix Table 1: Summary of potential alternative ECM data sources

| | Notes | Versus UK real-world data source |
|---|---|---|
| CINRG subset from research comparing patients receiving ECM with STRIDE registry data[6] | • Included in givinostat MAIC SA<br>• Included in NICE HST appraisal 22 to form an ITC comparing ataluren with ECM | • Data not as recent as the UK real-world data (patients recruited during 2 time periods: 2006–09 and 2012–16)<br>• Study was not conducted in UK centres |
| CINRG full population[33] | Excluded from analyses | • As per CINRG subset, older data and no UK centres<br>• In addition, some boys had participated in clinical trials of ataluren or had received eteplirsen, drisapersen or tadalafil; or they had missing data for age at LOA and age at first symptoms. These patients were excluded in the CINRG subgroup used for the givinostat MAIC SA (data reported in Mercuri 2023[6]) |
| North Star dataset for larger number of included centres, for example as reported in Zambon 2022,[16] and Stimpson 2024[17] | Excluded from analyses | • KM curves only available for ambulatory outcomes and not across multiple ambulatory and non-ambulatory outcomes<br>• Pick-and-mix of different cohorts of North Star patients and cut off dates would be required to include this data in the MAICs, with the potential to yield inconsistent findings across disease milestones |

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; ECM, established clinical management; HST, highly specialised technology; ITC, indirect treatment comparison; K-M, Kaplan-Meier; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; SA, sensitivity analysis; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

## Appendix Table 2: List of studies included in the clinical SLR based on the PICOS criteria relevant to the decision problem

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| **Givinostat studies** | | | | |
| E. Mercuri; J. J. Vilchez; O. Boespflug-Tanguy; et al. | 2024 | Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial | Not applicable – givinostat publication | The Company included all givinostat clinical trial studies for which patient-level data were available to inform the givinostat arm in the ITC (EPIDYS; Study 43; Study 51). These studies are not relevant for identifying ECM comparator data with a long follow up period (>18 months) |
| Eugenio Maria Mercuri, Claudia Brogna, Craig Zaidman, Katherine Mathews, et al. | 2024 | M163: The EPIDYS Givinostat Study in DMD: supportive results | Not applicable – givinostat publication | As above |
| Simonetta Andrea Licandro, Stefania Petrini, Krista Vandenborne, et al. | 2024 | S71: Givinostat effects on DMD pathogenesis | Not applicable – givinostat publication | As above |
| C. Mcdonald, L. Servais, F. Munell, et al. | 2024 | P369: Givinostat in Duchenne muscular dystrophy: effect on disease milestones | Not applicable – givinostat publication | As above |
| K. Vanderborne, R. Willcocks, G. Walter, et al. | 2024 | P370: Givinostat in DMD: results of the EPIDYS Study with particular attention to MR measures of muscle fat fraction | Not applicable – givinostat publication | As above |
| E. Mercuri, C. Brogna, J. Mah, et al. | 2024 | P371: Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA | Not applicable – givinostat publication | As above |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| K. Vandenborne; R. Willcocks; G. Walter; et al. | 2023 | Givinostat in DMD: results of the EPIDYS study with particular attention to MR measures of muscle fat fraction | Not applicable – givinostat publication | As above |
| E. Mercuri; C. Brogna; J. Mah; et al. | 2023 | Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA | Not applicable – givinostat publication | As above |
| C. McDonald; L. Servais; F. Munell; et al. | 2023 | Givinostat in Duchenne muscular dystrophy: effect on disease milestones | Not applicable – givinostat publication | As above |
| Eugenio Mercuri, Claudia Brogna, Jean K. Mah, et al. | 2023 | P99: Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA | Not applicable – givinostat publication | As above |
| Krista Vandenborne, Rebecca Willcocks, Glenn Walter, et al. | 2023 | P113: Givinostat in DMD: results of the EPIDYS Study with particular attention to MR measures of muscle fat fraction | Not applicable – givinostat publication | As above |
| E. Mercuri; J. Vilchez; O. Boespflug-Tanguy; et al. | 2022 | O.13 Givinostat in DMD: results of the EPIDYS Study | Not applicable – givinostat publication | As above |
| Paolo Umberto Bettica | 2022 | Update on the development of Givinostat in DMD | Not applicable – givinostat publication | As above |
| **Natural history studies** | | | | |
| Pietrusz A, Astin R, Guglieri M, et al. | 2024 | P39 The effect of corticosteroid treatment on pulmonary function in adults with Duchenne muscular dystrophy | Yes | Included in base case, multiple outcomes of interest reported for a UK cohort |
| Pietrusz A | NR | Natural history of DMD cohort attending Neuromuscular Service National Hospital for | Yes | Included, publication linked with study in row above |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| | | Neurology and Neurosurgery, Queen Square, London | | |
| Christian Werner, Shiwen Wu, Sheffali Gulati, et al. | 2024 | M166: Ataluren delays clinically meaningful milestones of decline in 6MWD in patients with nmDMD from Study 041, a phase 3, placebo-controlled trial | Ataluren study | Trial includes placebo arm but only short-term follow-up (72 weeks only) |
| Christian Werner, Eugenio Maria Mercuri, Francesco Muntoni, et al. | 2024 | T328: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Christian Werner, Már Tulinius, Filippo Buccella, et al. | 2024 | T327: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| G. Stimpson; D. Ridout; A. Wolfe; E. Milev; E. O'Reilly; A. Manzur; A. Sarkozy; F. Muntoni; T. J. Cole; G. Baranello | 2024 | Quantifying Variability in Motor Function in Duchenne Muscular Dystrophy: UK Centiles for the NorthStar Ambulatory Assessment, 10 m Walk Run Velocity and Rise from Floor Velocity in GC Treated Boys | Participants from the UK NorthStar registry | Outcomes not of interest for economic model and no baseline characteristics reported; includes assessment only up to 16 years (when boys start to transition to adult services) |
| E. Mercuri; F. Muntoni; F. Buccella; et al. | 2023 | Age at loss of ambulation in patients with DMD from the STRIDE registry and the CINRG natural history study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| E. Mercuri; A. N. Osorio; F. Muntoni; et al. | 2023 | Correction to: Safety and effectiveness of ataluren in patients with nonsense mutation DMD in the STRIDE Registry compared with the CINRG Duchenne Natural History Study (2015-2022): 2022 interim analysis | Yes. STRIDE vs CINRG | Erratum to main paper that is included in the ITC (see below) |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| J. Broomfield; K. Abrams; N. Latimer; et al. | 2023 | Natural history of Duchenne muscular dystrophy in the United Kingdom: A descriptive study using the Clinical Practice Research Datalink | CPRD (Clinical Practice Research Database): GOLD and Aurum | No baseline characteristic data available; no outcomes of interest |
| V. Laugel; S. D. Lucia; J. Davion; et al. | 2023 | Preliminary Results from a Prospective, Multicentric, Follow Up Standardized Cohort to Assess Natural History of Duchenne muscular dystrophy | The analysis includes 48 patients with at least 6 months follow up (mean=13.5 months) from France and UK | Conference abstract with insufficient detail |
| M. Tulinius; F. Buccella; I. Desguerre; et al. | 2023 | Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE registry and CINRG natural history study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| E. Mercuri; A. N. Osorio; F. Muntoni; et al. | 2023 | Safety and effectiveness of ataluren in patients with nonsense mutation DMD in the STRIDE Registry compared with the CINRG Duchenne Natural History Study (2015-2022): 2022 interim analysis | Yes. STRIDE vs CINRG | Included in ITC, multiple outcomes of interest reported for the subgroup of CINRG patients |
| Pannie (Panayiota) Trifillis, Eugenio Mercuri, Francesco Muntoni, et al. | 2023 | P186: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Christian Werner, Már Tulinius, Filippo Buccella, et al. | 2023 | P116: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Christian Werner, Már Tulinius, Filippo Buccella, et al. | 2023 | EPNS23-2070: Pulmonary function in patients with Duchenne muscular dystrophy from the | STRIDE vs CINRG | Conference abstract with insufficient detail |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| | | STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | | |
| Panayiota Trifillis, Eugenio Mercuri, Francesco Muntoni, et al. | 2023 | EPNS23-2064: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis | STRIDE VS CINRG | Conference abstract with insufficient detail |
| C. M. McDonald; F. Muntoni; V. Penematsa; et al. | 2022 | Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients | Study 019 (ataluren) vs CINRG | Small subgroup of CINRG patients matched with ataluren Study 019; Mercuri 2023 CINRG dataset preferred due to larger number of included patients |
| D. Machado; E. de Paula; T. Márcia; et al. | 2022 | CO105 Long-Term Benefit of Ataluren Treatment in Non-Sense Duchenne muscular dystrophy Versus Standard of Care | Ataluren (STRIDE vs CINRG and Study 019 vs CINRG) | Conference abstract with insufficient detail |
| Pannie Trifillis, Francesco Muntoni, Már Tulinius, et al. | 2022 | P98: Comparison of North Star Ambulatory Assessment score change in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial | STRIDE vs Study 020 NCT01826487 | Conference abstract with insufficient detail |
| E. Mercuri; F. Muntoni; F. Buccella; et al. | 2022 | P22: Age at loss of ambulation in patients with DMD from the STRIDE registry and the CINRG natural history study: A matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Pannie Trifillis, Eugenio Mercuri, Francesco Muntoni, et al. | 2022 | P97: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Pannie Trifillis, Már Tulinius, Filippo Buccella, et al. | 2022 | P99: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| Craig McDonald, Claudio L. Santos, Rich Able, et al. | 2022 | P110: Associations Between Daily Deflazacort or Prednisone and Ages at Disease Progression Milestones Among Patients with Duchenne muscular dystrophy (DMD) | PRO-DMD-01 and CINRG natural history studies | Conference abstract with insufficient detail |
| M. Tulinius; F. Buccella; I. Desguerre; et al. | 2022 | P.23 Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| A. A. Zambon; V. Ayyar Gupta; D. Ridout; et al. | 2022 | Peak functional ability and age at loss of ambulation in Duchenne muscular dystrophy | UK NorthStar Network | Only ambulation-related outcomes reported; thus Pietrusz subgroup preferred as a consistent set of data reporting both LOA and respiratory outcomes |
| E. Mercuri; F. Muntoni; A. N. Osorio; et al. | 2020 | Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study | STRIDE vs CINRG | Contains subgroup of dataset reported in Mercuri 2023 that was included in the ITC (STRIDE vs CINRG) |
| C. M. McDonald; H. Gordish-Dressman; E. K. Henricson; et al. | 2018 | Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history with and without glucocorticoids | CINRG alone (GC > 1 year vs GC naïve) | Outcomes of interest not reported |
| C. M. McDonald; E. K. Henricson; R. T. Abresch; et al. | 2018 | Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study | CINRG (NCT 00468832) | Subgroup of CINRG patients reported in Mercuri 2023 preferred as some restrictions applied to the Mercuri dataset, which enabled a more balanced comparison with the givinostat data. For example, 22 CINRG patients were excluded because they had participated in clinical trials of ataluren or had received eteplirsen, drisapersen or tadalafil; 20 patients were also excluded because they had missing data for age at loss of ambulation and age at first symptoms |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| V. Ricotti; D. A. Ridout; M. Pane; et al. | 2016 | The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials | UK NorthStar Network + data from 172 Italian boys with DMD | Outcomes not of interest; no Kaplan-Meier curve for age at LOA |
| L. Bello; H. Gordish-Dressman; L. P. Morgenroth; et al. | 2015 | Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study | CINRG-DNHS | Outcomes not of interest (LOA by steroid regimen for all enrolled CINRG patients) |
| G. Schram; A. Fournier; H. Leduc; et al. | 2013 | All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy | Retrospective cohort study on patients with DMD treated with renin-angiotensin-aldosterone system antagonists with or without steroid therapy | Outcomes not of interest (mortality and CV events) |
| V. Ricotti; D. A. Ridout; E. Scott; et al. | 2013 | Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy | NorthStar UK database (17 neuromuscular centres in the UK) | Only ambulation-related outcomes considered; thus Pietrusz subgroup preferred as a consistent set of data reporting both LOA and respiratory outcomes and reports more recently collected data, and therefore more likely to reflect current treatment practise |
| C. M. McDonald; E. K. Henricson; R. T. Abresch; et al. | 2013 | The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study | The natural history data were derived from the placebo arm of a phase 2b, international, multicentre, randomised, double-blind, placebo-controlled, dose- | Short follow-up, 48 weeks only |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| | | | ranging study to evaluate the efficacy and safety of ataluren in ambulatory male patients aged ≥5 years with nonsense mutation DMD | |
| E. K. Henricson; R. T. Abresch; A. Cnaan; et al. | 2013 | The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures | CINRG | No outcomes of interest; short follow-up, 12 months only |
| **Update review (November 2024)** | | | | |
| **Givinostat** | | | | |
| D. Vučinić; A. Nascimento; R. Finkel; et al. | 2024 | Short-term and long-term safety profile of Givinostat in Duchenne muscular dystrophy | Not applicable – givinostat publication | The Company included all givinostat clinical trial studies for which patient-level data were available to inform the givinostat arm in the ITC (EPIDYS; Study 43; Study 51). These studies are not relevant for identifying ECM comparator data with a long follow up period (>18 months) |
| D.G. Andres; V. Sansone; H. Phan; et al. | 2024 | Givinostat in Duchenne muscular dystrophy: natural history comparison applying propensity score matching | Not applicable – givinostat publication | As above |
| **Natural history** | | | | |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
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| **Original SLR (May 2024)** | | | | |
| G. Stimpson: D. Ridout; A. Sarkozy; A. Manzur; et al. | 2024 | Relationship between growth and ambulation loss in Duchenne muscular dystrophy boys on steroids | UK NorthStar database | Age at LOA only outcome of interest reported; thus Pietrusz subgroup preferred as a consistent set of data reporting both LOA and respiratory outcomes |
| M. Van Der Holst; M. Italianer; A Wolfe; et al. | 2024 | Is upper extremity contracture progression related to changes in upper extremity function in Duchenne muscular dystrophy? An international multicenter natural history study | International multicentre natural history study | Conference abstract with insufficient detail |
| V. Laugel; A. Seferian; J.B. Davion; et al. | 2024 | Preliminary results from a prospective, multicentric, follow up standardized cohort to assess natural history of Duchenne muscular dystrophy | France and UK natural history data (48 patients) | Conference abstract with insufficient detail |

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; GC, glucocorticoid; MR, magnetic resonance; nm, nonsense mutation; MR, magnetic resonance; NR, not reported; NSAA, North Star Ambulatory Assessment; SLR, systematic literature review; STRIDE, Strategic Targeting of Registries and International Database of Excellence; UK, United Kingdom.

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NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

**Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]**

**Clinical expert statement and technical engagement response form**

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

**Please note, part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 6 May 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# Part 1: Treating Duchenne muscular dystrophy and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

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| **1. Your name** | [redacted] |
| **2. Name of organisation** | [redacted] |
| **3. Job title or position** | [redacted] |
| **4. Are you (please tick all that apply)** | ☐ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with Duchenne muscular dystrophy ?<br>☒ A specialist in the clinical evidence base for Duchenne muscular dystrophy or technology?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☐ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☒ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | I have no current or past links - direct or indirect with the tobacco industry |
| **8. What is the main aim of treatment Duchenne muscular dystrophy?** | At this time, in the absence of any curative treatment, the aim is to slow down the rate of decline in muscle weakness preserving independent mobility and |

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| (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | function for as long as possible. This includes maintaining ambulation, upper limb function, trunk control and respiratory function to optimise quality of life.<br>The pattern of muscle weakness in 'untreated' DMD is predictable - although the rate of decline varies between individuals - with some have a more rapid progression than others (PLOS One paper, Muntoni et al 2019)<br>Muscle weakness is most prominent initially in the proximal muscles affecting the pelvic girdle > shoulder girdle, followed by involvement of trunk, respiratory and then distal muscles.<br>Development of cardiomyopathy is inevitable over time, but the onset of significant cardiac impairment varies between individuals and does not relate directly to motor function milestones<br>Key milestones in disease progression are as outlined by Project Hercules and other natural history publications:-<br>• Loss of ability to rise from the floor<br>• Loss of ambulation<br>• Loss of ability to stand and transfer independently<br>• Loss of hand to mouth function and onset of respiratory/truncal muscle weakness<br>• Loss of hand function and ability to operate controls, usually paralleled by increased respiratory muscle weakness<br><br>Reducing the speed at which muscle weakness/wasting progresses delays the time/age at which the sequential loss of each element of function occurs<br>This is seen with the use of corticosteroids which delay ambulation in the 1st instance with subsequent delay in the development of truncal and respiratory muscle weakness. This is evidenced by the reduced number of Children and young people (CYP) with DMD requiring scoliosis surgery and a delay in the age at which ventilatory support is required. In turn, this has been associated with improved life expectancy and quality of life with young men having less |

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| | impairment at critical times of development - optimising social and academic engagement, with benefits in overall participation and wellbeing.<br><br>Thus, although the focus of intervention may be delaying the loss of ambulation, it is established that this has benefits in delaying onset of other muscle weakness and loss of independent functioning.<br><br>In conjunction with the goal of slowing down the rate of decline in muscle function, management aims to optimise inclusion and minimise the secondary effects of muscle weakness. A multidisciplinary approach is required and must consider the physical, emotional and social well being of both the affected individual and their family.<br><br>The impact of caring for a CYP with DMD cannot be underestimated and any intervention which slows down disease progression and preserves function and well being is hugely significant for both affected individuals and their loved ones |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | Slowing down the 'rate' of an individual's decline to any meaningful degree is a significant benefit.<br>Natural history studies and clinical trials have outlined the median age and range at which a particular milestone occurs in DMD. However, the impact of change in an individual's disease course is inevitably lost when assessing the impact across a larger group and whilst the overall change in a large cohort of patients might appear small, the significant impact on specific individuals is often lost.<br><br>For example, in the 25 years that I have been managing CYP with DMD in Yorkshire, there has been a significant change in the DMD cohort as a result of the routine use of corticosteroids (CS) |

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| | The evidence from natural history cohorts is that use of CS delays the 'average' loss of ambulation from 10.5 yrs to somewhere between 12.5 and 14 yrs depending on whether intermittent or daily CS are used.<br>On a practical level in 2000 when I took over the service, the majority of boys with DMD lost ambulation in primary school and made up 85% of those children with neuromuscular disorders requiring spinal surgery for neuromuscular disease-related scoliosis and were typically requiring overnight ventilatory support in mid teens<br>Now, it is rare to see a lad with DMD not walking as they 'transition' to high school, less than 5% of scoliosis surgery in CYP with NM disorders is for DMD and only a handful of the young people with DMD who remain in our service, which typically includes those up to 19 years of age, have required ventilatory support. This is real life evidence of the knock on impact of delaying disease progression in terms of loss of ambulation on other muscle function associated with improved morbidity and mortality in DMD. |
| **10. In your view, is there an unmet need for patients and healthcare professionals in Duchenne muscular dystrophy?** | Yes<br>DMD remains a life limiting multisystem disease with significant impact on the quality of life of affected individuals, their families and communities.<br><br>Similarly, the health care costs of managing an individual are considerable given the multisystem nature of the disease.<br>Affected individuals require regular input from neuromuscular (NM) clinicians and specialist NM therapists and nurses, as well as specialist respiratory teams and physiotherapists with expertise in long term ventilation, cardiologists, gastroenterologists, dieticians, orthopaedic and spinal surgeons, endocrinologists and opthalmologists on a regular basis<br>All patients need specialist adaptations and equipment including specialist wheelchair provision, orthotics and home equipment to support moving and handling.<br>The majority will require additional care packages to support access to education and many also have social care/respite needs |

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| | As the condition progresses, young men require support with mobility and all their self care, placing a huge burden on families/carers who strive to meet these physical needs on the background of the emotional, financial and social burden of providing this level of care to a child/loved one with a limited life expectancy<br><br>There is therefore considerable unmet need for both the individual and their carers as well as a significant burden on health, education and social services. |
| **11. How is Duchenne muscular dystrophy currently treated in the NHS?**<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)<br>• What impact would the technology have on the current pathway of care? | The care of those with DMD in the UK has been more structured and consistent than in many similar progressive life limiting conditions<br><br>This has been driven by the development of a multidisciplinary clinical network the 'Northstar' network led by the team at the Dubowitz centre based at GOS. The network was initially developed to encourage a standardised approach to the use of corticosteroids and was first supported by charitable funding from MDUK, and subsequently with some investment from industry.<br><br>The Northstar network brings together the 23 paediatric 'Northstar' centres across the UK and has facilitated the development of internationally recognised assessment tools - in particular the North Star Ambulatory Assessment tool (NSAA) and a standardised approach to the clinical assessment and management of DMD in the UK. The vast majority of CYP with DMD are managed within Northstar centres, and have regular and standardised clinical and physiotherapy monitoring every 6- 12months. Data is pseudo anonymised before being uploaded and stored in the secure Northstar database. As corticosteroid use and application of recommended standards of care have improved life expectancy there are more adults living with DMD in UK. Their care is coordinated by the 25 'adult' Northstar centres who undertake and record adult-focused standardised assessments, capturing progress and complications in adults with DMD in the UK |

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| | Within Northstar centres > 95% of DMD patients are enrolled in the Northstar project ensuring a standardised approach to care<br>This approach was further strengthened by the publication of updated international recommendations for care in 2018 and the subsequent development of the DMDCare UK project which has brought together specialist NM clinicians, patients, Patient advisory groups (PAGS) and relevant stakeholders to ensure 'best possible care for all those with DMD in the UK' by updating the 2018 standards in light of new evidence and patient priorities to produce guidance that is relevant and applicable in a UK health care setting.<br>The Northstar network and DMD Care UK meet regularly to discuss developments in standards of care and to support their implementation across the UK.<br><br>As with other new technologies and interventions in DMD, the Northstar network would work to implement Givinostat in a fair and equitable way, ensuring that the risks and benefits of treatment were captured as accurately as possible through the database to inform future management<br><br>Now that MHRA have licensed Givinostat there is an SmPC in place which outlines the safety monitoring required. This is extensive and mandates a minimum of 8 blood tests and 3 ECGs in the 1st year of treatment over and above those currently recommended for routine monitoring in DMD. Coordinating these blood tests, chasing and acting on results and providing advice and support for those experiencing adverse effects from treatment will have a considerable burden on neuromuscular centres. This has impeded the uptake of the Italfarmaco "Extended Access Programme (EAP)' in the UK. This is due to the potential enrolment of multiple patients at each Northstar site with a dramatic increase in workload for the NM teams. However, the incidence of adverse events and need for intervention and monitoring dose reduce after the 1st year of treatment and rolling out Givinostat as part of standards of care, once |

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| | the prevalent population is established on treatment should be more manageable and sustainable. |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care?<br>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | As noted above, the SmPC details a specific safety monitoring plan for regular blood tests and ECGs, particular in the 1st 6-12 months of treatment. There are also requirements for additional ECGs.<br>These will need to be coordinated over and above current standards of care - with treating teams able to act on results or adverse events from treatment in a timely manner.<br>In Leeds, where we have around 40 patients eligible for the EAP, we have estimated that it would require a full time band 5 CNS to coordinate, monitor and follow up on all the blood tests, in addition to providing advice and support for those with adverse events ( up to 30% experiencing vomiting or moderate to severe diarrhoea in the clinical trials ) while ensuring dose modifications/treatment pauses occur in a safe and timely manner.<br><br>However, this need for a full time nurse reflects the additional resources required to initiate treatment in many eligible boys at the same time. Once the drug is available as part of standards of care and the prevalent population have been established on a stable dosage, the additional burden on centres will be 'spread out' in a more manageable fashion.<br><br>The additional resources needed will depend on the number of patients eligible for treatment once the technology is approved and the agreed timeframe over which the drug is expected to be started. To implement Givinostat as a new treatment across all eligible patients within a 3 month timeframe should NICE approve its use, will required additional medical, nursing and pharmacy resources at treating sites, at least in the 1st 2 years. |

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| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | The evidence from the RCT and OLE studies suggests that Givinostat has a genuine impact on muscle function. The primary end point of the RCT was difference in a timed functional measure - the 4 stair climb. After 18m on treatment, boys receiving Givinonstat did do this more slowly than at baseline but were significantly faster than the boys in the control group. The median time difference in the task between treated and control groups at the end of the study was 1.8 secs.<br>There was also a significant difference in the secondary endpoints derived from the NSAA score and in the fat content of muscles on MR imaging<br><br>Whilst the progression of DMD does vary between individuals, with some boys demonstrating a faster decline than others (Muntoni et al PLoS One Sept 2019) the pattern of progression is predictable across all affected individuals, as mapped out by the Hercules project.<br>As the proximal muscles are most affected initially - the ability to climb stairs and to rise from the floor are the 1st skills lost in boys with DMD, followed by increased difficulty in walking before loss of ambulation, with subsequent loss of upper limb and truncal muscle function, before the onset of respiratory muscle weakness which has been shown to occur at the same time as the loss of hand to mouth function. .<br>A number of studies have analysed natural history datasets and used this data to plot the actual decline in functional ability and derive minimal clinically important differences in timed function tests.<br>These studies (Muntoni et al PLoS One July 2024) indicate that a difference of > 1.3s in time for 4 stair climb represents a clinically significant change as preserving ability to climb stairs reflects preservation in proximal muscle power.<br><br>There is good evidence from natural history databases that maintaining early ambulatory skills (climbing stairs and rising from the floor) is associated with a later age at loss of ambulation and in turn later loss of upper limb and respiratory function, with improved life expectancy |

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| | This is the pattern seen when comparing the disease trajectories of boys receiving corticosteroid treatment with historical controls. Initially it was only possible to demonstrate a delay in loss of ambulation but as the cohort treated with steroids grew older, it was possible to demonstrate a parallel preservation in arm, trunk and respiratory muscle function with steroids with treated patients requiring ventilatory support later in life, a reduced need for scoliosis surgery and improved life expectancy.<br><br>Thus, a drug that preserves muscle function to a level that is sufficient to impact the ability to climb stairs would be expected to have an impact on other motor functions including ambulation. If the benefits are maintained over time which appears to be the case in the long term extension studies, such that treated boys have a slower rate in the decline of their muscle function, it would be expected to have a similar impact on slowing decline in upper limb and respiratory function. In addition to improving life expectancy, preserving fine motor skills improves quality of life as such skills are essential for operating wheel chair controls and keyboards necessary to maintain independence. Maintaining hand to mouth function enables independence in feeding and delaying onset of respiratory muscle weakness reduces need for ventilatory support until later in life.<br><br>In the absence of curative treatment, the combination of Givinostat and corticosteroids appears to convey genuine benefit to ambulant patients irrespective of their particular genotype, unlike many of the other drugs in clinical trial. The impact of steroids in slowing muscle decline in DMD has been considerable and shown benefits in both quality and quantity of life and the evidence suggests that givinostat could have an additional benefit in DMD. |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | Unlike other many other compounds being studied in DMD, Givinostat can be used in all boys with DMD irrespective of their underlying genotype. This is clearly positive for the DMD community.<br>To date the evidence of its benefit is limited to ambulant boys > 6 years of age, but there is no biological reason to suggest that similar benefits will not be seen in older, non ambulant boys, although the data from the Ulysses trial in non |

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| | ambulant boys is not yet available. Similarly, data from younger boys is currently being collected in multicentre studies<br><br>Whilst the drug appears generally well tolerated, there were some boys in the clinical trial who developed moderate to severe side effects requiring dose reduction or discontinuation.<br>Data from the trial suggested that boys receiving lower doses of medication demonstrated similar benefits to those on 'full' dosing, but this will need to be tested in the 'real world'<br>There may be some boys who cannot tolerate the recommended safety monitoring as a result of behavioural difficulties with repeated blood tests |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?**<br>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | Those starting Givinostat will require additional monitoring and investigations as outlined by the MHRA in the SmPC. There are regular blood and ECG tests required with a minimum of 8 blood draws in the 1st year, and 4 ECGs. These tests are over and above the recommended standard of care, with boys currently being reviewed every 6 m and typically having 1 set of blood tests/year<br>If blood tests are abnormal on treatment with Givinostat (as seen in around 30% of those in clinical trial) the tests will need to be repeated and dosing titrated or discontinued as a result<br>In addition, up to 30% of treated boys had moderate to severe GI dysfunction and thus will need advice and support regarding their management<br><br>Individual centres will need sufficient resources to undertake the necessary discussions with patients and families, ensure robust safety monitoring and effective drug titration. This will require additional nursing, medical and pharmacy time. The burden is highest in the 1st year of treatment, after which a suitable tolerable dose can be continued with less frequent intervention.<br><br>Given the number of tests required, and the importance of safety monitoring, there will be some more families who may struggle with the process. It will |

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| | important to ensure equitable access to treatment irrespective of geography and other social/cultural factors. Some families will not have the resources to plan and engage in the required monitoring and they will need additional follow up and support from their treating centres. This level of additional support is not currently available within most centres, other than at the expense of other necessary clinical activities. In addition, many boys/young men find blood tests particularly challenging, in part as consequence of their DMD with skin change/muscle contractures and in part as a result of the behavioural phenotype seen in DMD. These lads may require additional support for blood tests - play therapy/VR which is only available in certain centres. |
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | Any boy/young man experiencing adverse events not responding to dose reduction will be withdrawn from treatment<br>If the impact of givinostat is shown to be sustained over time and to result in the expected preservation of upper limb, trunk and respiratory muscle function then it is hard to suggest a point at which the drug should be discontinued, assuming that both the treating clinician and patient feel continued use is in their best interest |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | As noted in previous TA for DMD (Vamolorone and Ataluren), measuring QofL in DMD is challenging.<br>In particular, capturing meaningful patient outcome measures is not done routinely in practice. Tools used in other conditions, such as EQ-5D do not correlate well with mobility defined 'health states' in DMD.<br>Given the increasing dependence on carers as the condition progresses, the impact of a drug that slows the rate of disease and need for support with self care is considerable on families. Again, capturing this with conventional tools has proved extremely challenging. |

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| | A key consideration is the fact that maintaining mobility and independence in the teenage years can have added benefits outside physical health. Being able to participate in educational and social activities as a result of better health in adolescence has knock on benefits on overall well being - increasing the chance of engaging in higher education/work and inclusion in other social activities, reducing isolation and low mood.<br><br>The oral delivery of a drug in DMD, irrespective of a patient's genotype is an important consideration and this, together with the MHRA, FDA and EMA approval has been very positive for the DMD patient community. |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?**<br>• Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | It is difficult to quantify the potential long term improvements from Givinostat. Rather than a step change, its impact is more like that of steroids - delaying the onset of muscle weakness and shifting the 'curve' of stepwise functional loss further to the right.<br><br>Much research effort in DMD has focused on increasing the amount of functional dystrophin in the muscle. However this technology, including exon skipping studies and the micro/mini dystrophin gene studies are not applicable to all patients with DMD and preclude use in large number of the DMD community, unlike Givinostat.<br>The improvements seen in patients receiving Givinostat are comparable, if not better, than those seen in exon skipping/microdystrophin trials to date. |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | I have commented on requirements and challenges of safety monitoring and adverse events above. |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting? | Yes<br>The majority of ambulant boys with DMD receive oral steroids and are followed within the 23 Northstar sites. Boys are seen 6 monthly and have standard clinical assessments including NSAA and timed tests. The 4 stair climb is not routinely used in clinical practice but other studies have shown that the change in 4 stair |

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| • What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | climb mirrors other functional changes in particular timed rise from the floor and other elements of the NSAA score.<br>The data is then uploaded to the Northstar database hosted by Certus and can be used to evaluate progress over time.<br><br>As noted, there is evidence to support the fact that slowing down the loss of ability to climb stairs is meaningful for patients and correlates with other motor function that is captured routinely in clinical care<br><br>I am not aware of any adverse events, but the Italfarmaco Extended Access Programme includes a commitment to adverse event reporting and this, if adopted, and data from other countries where Givinostat has been incorporated into clinical practice, will need to be closely monitored. |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | As noted above, there will be data from the Ulysses study providing better understanding of the risks and benefits in non ambulant boys/adults with DMD in addition to the clinical trial looking at safety/impact in those < 6 years of age, however this will not be available at the time of the committee meeting<br>There may be additional data from other countries where the drug is now available and/or the UK EAP |
| **22. How do data on real-world experience compare with the trial data?** | I am not aware of any specific publications detailing the use of Givinostat in other countries but this may become available via abstracts/presentations at international conferences |
| **23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.** | I have noted the potential challenges for some sections of the DMD community in answer to Q15<br>There will be some families who do not have the resources to engage in the required monitoring - as a result of geographical, social and cultural differences. It will be important to ensure equitable access to treatment for all boys who might benefit irrespective of their family's situation. This is likely to require additional planning and input from NM and community nurses and social care. |

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| Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this evaluation could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

# Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

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| **Have comparators been appropriately specified in the submission? (Sections 2.1 and 2.2 of EAR)**<br>This is about the consideration of vamorolone which may displace current corticosteroid use in established clinical management following publication of NICE guidance recommending use of vamorolone in Duchenne muscular dystrophy in January 2025.<br><br>What proportion of people have vamorolone instead of standard | In my view this is not a relevant issue for discussion.<br>Vamorolone is a corticosteroid with a completely different mechanism of action to Givinostat. Steroids have a recognisable impact on muscle function and cumulative benefits were seen in the Epidys study<br>Vamorolone would NOT be considered as an alternative to Givinostat<br>Vamorolone was not available as an 'approved' corticosteroid at the time of the Epidys study, and therefore has not been 'tested' in conjunction with Givinostat. However, there is no reason to suggest that it would impact the action of an HDAC inhibitor any more or less than either prednisolone or deflazacort. Thus the numbers of boys taking Vamorolone, instead of prednisolone or deflazacort, should not have any impact on the decision to use Givinostat. Neither would there be any anticipated impact on the benefits or side effects of Givinostat. The recommendations for safety monitoring and impact on the patients and treating centres would be exactly the same. |

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| corticosteroids? How would this proportion be expected to change over time?<br>What impacts whether people have vamorolone rather than standard corticosteroids?<br><br>How does the clinical effectiveness of vamorolone compare with standard corticosteroids such as prednisone? | The only situation where there may be any change in recommended care, would be in a patient where consideration was being given to starting or 'switching' to Vamorolone at the same time as starting Givinostat. There is no absolute contraindication to this, but in discussions with the North star network it was agreed that it would be advisable to initiate one drug at a time i.e 3-6 months apart, so that it is possible to determine that an adverse effect or benefit relates to a particular 'new' treatment. This would be the case for all those with DMD starting on steroids - irrespective of the choice of steroid drug.<br><br>NICE have already explored the role of Vamorolone and how it correlates with other conventional corticosteroids in a separate technology appraisal (TA 1031) and I do not think there is any value in repeating the process as it has no impact on the appraisal of Givinostat. |
| **Definition of 'ambulant' status and implications for generalisability to UK clinical practice (Sections 2.2, 3.3.1.2, 3.3.2.2, 3.4.2.1, 3.4.2.2 of EAR)**<br>How are the following terms defined in people with DMD in NHS practice?<br>• 'ambulant'<br>• 'non-ambulant' | The progressive decline seen in DMD has been described in a number of publications. The subdivisions of early and late ambulatory and non ambulatory states were outlined in the 2009 recommendations of care published by Bushby et al in the Lancet, with different priorities for intervention and management described for the different stages of disease<br><br>The definition of the ambulatory v non ambulatory states is somewhat 'nuanced' in different settings, with a more precise definition required for clinical trials, which typically define those boys/young men with an inability to walk for 10m independently as 'non ambulant'. Clinical trials of ambulant boys are typically aimed at those within either the 'early' or 'late ambulatory' phase. |

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| • 'late ambulant'<br>• 'early non-ambulant'<br>What clinical measures are used for ambulatory or functional status in DMD in NHS practice?<br>How do these measures differ from what may be used in clinical studies? | Thus inclusion criteria often specify a specific 6 minute walking distance or 'cut off' for timed tests ie rise from floor or as in Epidys the 4 stair climb, in order to ensure participants fall within the early or late ambulatory stage depending on the aim of the study.<br><br>However, in clinical practice and in the minds of patients/families the loss of ambulation is more absolute and correlates with 'continuous wheelchair use' and the inability to take any steps with support. This definition correlates more closely with the 'transfer' state rather than the 'early non ambulant health state' defined by project Hercules. The latter being defined as the inability to support weight in standing for 3 seconds.<br><br>This more 'broad' definition of loss of ambulation as the inability to stand for > 3s has been used in clinical settings - for example as a stopping criteria for the use of Translarna under the NHSE managed access agreement, which was only 'approved' for use in ambulant patients and as an inclusion criteria for enrolment in the Givinostat EAP.<br><br>Publications from the CINRG database define loss of ambulation as 'participant or care reported age at continuous wheelchair use to the nearest month, validated by trained evaluator confirming an inability to walk 10m independently". Publications from CINRG suggest a median age of LofA of 14 yrs in those taking oral steroids, though do not look at the specific dose regimes or other factors that might contribute to this.<br><br>In publications from the Northstar group (Ricotti et al 2012) those boys scoring 0 on item 2 'walk' of the Northstar Ambulatory Assessment (NSAA) were defined as having lost ambulation. In 2012, analysis of the dataset revealed a median LofA of 12 years in those taking intermittent and 14.5 years for those using daily steroids.<br><br>Subsequent publications have looked at total NSAA and determined that those with score < 5 can be classified as non ambulant<br><br>Recent publications have highlighted the variability in disease progression within the DMD population. In PLoS One publication in September 2019 Muntoni et al analysed the rate of |

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| | decline in Northstar score from 9 sources and were able to separate boys into 4 different disease trajectories with 25% in the group rapidly losing function (Gp1), achieving a NSAA < 5 at 10 yrs and 20% in the most slowly progressive group (Gp 4) not achieving a NSAA of < 5 yrs until 15 yrs of age.<br><br>Work from the same group (Muntoni et al PLoS One October 2024) has now characterised patients with DMD across the health states defined by Project Hercules. The 'lower' age of those in the 5 'non- ambulatory states' was 13 years which is compatible with the data used in modelling the natural history of UK patients.<br><br>The definition of the early and late non ambulatory phase has been helpful in identifying those patients at risk of additional complications as a result of loss of independent upper limb function, reduced respiratory muscle strength and poor bulbar function. The inability to raise a hand to the mouth has been shown to correlate with significant reduction in FVC% and a higher risk of requiring ventilatory support. Loss of arm function increases need for carer support as it becomes more difficult to feed independently and operate controls.<br><br>Project Hercules defined 5 non ambulatory states to highlight the additional care needs of both limited fine motor skills and the need for ventilatory support during the night and then continuously.<br><br>In clinical practice, evaluation of upper limb function in non ambulant patients is measured using standardised assessments - the Brook scale, EK2 scale and PUL assessment. The simple Brook scale can be applied without specific equipment or clinic time with a score of 3 indicating a higher risk of respiratory impairment and the need for further specialist assessment to evaluate the need for ventilatory support and/or further adaptations. Typically those with lack of Hand to mouth function (Brook 3) would be defined as being in the late ambulatory stage.<br><br>In clinical practice, there are some patients with severe cognitive and behavioural impairment as a result of their DMD who cannot cooperate reliably with standard functional assessments, despite the skills of very experienced of neuromuscular physiotherapists. Their functional state |

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| | is therefore judged on carer history and observation and will be less precisely defined until the ability to take any steps is clearly lost.<br><br>Thus the milestones used for the company's economic model appear relatively consistent with the published ages at which key milestones are achieved. The analysis of the data from 3 UK adult centres treating those with DMD is likely to be representative of UK practice though has advantages and disadvantages. On the one hand it is possible to define median ages of later milestones including death and time at which full time ventilation is introduced, but on the other hand, there is a 'hisotorical' element to clinical management with a proportion of patients treated before use of corticosteroids became standard of care for ambulatory patients (2009) or was recommended for use in non ambulant patients (2018) in international guidance.<br><br>Thus the median ages quoted for LOA of 12.1 years and age at starting ventilation of 16.0 years are likely to be at the lower 'range' of what is now seen within the paediatric northstar centres in the UK. However, there are a cohort of patients ( see above) who do decline more rapidly and lose ambulation at an even earlier age of 10 years. |
| **Post-hoc selection of givinostat OLE patients (section 3.4.2.1 of EAR)**<br>This is about the patient population used in the open label extension study (OLE). The OLE population included people who had received givinostat in the initial study ("givinostat" group), people who received placebo in EPIDYS ("delayed givinostat") | It would be anticipated that those randomised to receive Givinostat from the beginning of the RCT would have greater benefits, given the results of the clinical trial, than those in the original 'placebo' group who did not receive Givinostat until the end of the trial<br><br>Given that the baseline characteristics of the treated and placebo group were the same but the NSAA and timed tests were less 'good' in the placebo group at the end of the study, this would be anticipated to 'dilute' the positive benefits seen in the OLE group<br><br>The 'treated' givinostat group were subdivided based on pre determined MR criteria and only data from those in group A with a fat fraction between 5-30% were used for comparative analysis with the placebo group. This subdivision was based on clinical consensus in order to |

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| and people who met the criteria for EPIDYS but were not enrolled ("naïve givinostat").<br><br>How might the efficacy of givinostat differ when excluding people who received placebo in EPIDYS ("delayed givinostat"), compared with including the full OLE population? | ensure that there would be a measurable change in the 'treated' group in comparison to the placebo group which was subdivided using the same MR criteria. Those randomised to the treatment arm but not meeting the 'MR criteria' were also given givinostat in order to collect additional safety data but their results were not used in the comparative analysis.<br><br>All boys were then enrolled in the OLE.<br><br>Boys receiving givinostat with more or less advanced dystrophic muscle change (naïve givinostat), as defined by MR fat fraction of > 30% and <5% respectively, might be expected to have a different pattern of response to those in the intention to treat group. Boys later in the disease course may not be able to demonstrate the same improvements in lower limb function but could see benefits in upper limb/trunk function which were not evaluated in the Epidys study but could be measured in the OLE group. As noted above, treatments that delay the age at which early disease milestones are reached also have an impact on later milestones including loss of arm function and decline in FVC%.<br><br>Similarly protecting the muscles of those with less dystrophic change may have a greater benefit with further delay in loss of key milestones, though more time is needed to demonstrate these changes in those with a more slowly progressive disease course<br><br>Overall it is difficult to predict exactly how the OLE will diverge from a natural history cohort of steroid treated DMD patients but as when comparing steroid treated with steroid naïve patients, the trajectories would be anticipated to diverge further with time, although further data is required to plot out the 'extent' or size of the change and the impact on different disease milestones.<br><br>Data from the Ulysses study and trial in younger patients will provide further information on outcomes in those patients who have milder/more severe disease progression. |
| **Source of data to inform comparative treatment efficacy (Section 3.4.2.2 of EAR)**<br>This is about how the data used for comparative treatment efficacy | Comparison with relatively short trial data and natural history studies is challenging in DMD, and there are no 'ideal' comparators that address the full range of difficulties in DMD<br><br>The CINRG dataset comprises a cohort of 400 patients enrolled between 2006 and 2016 and included both steroid naïve and steroid treated patients from 21 centres in 8 countries, 2 of |

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| in established clinical management may be imbalanced in prognostic factors such as baseline characteristics, type of corticosteroids and inclusion criteria for trials/registry studies compared with the givinostat clinical trial data.<br><br>Which of the following patient populations is likely to be most similar to the patient population in the EPIDYS clinical trial and OLE?<br>• UK registry study<br>• CINRG DHNS registry<br>What are the similarities and differences between these patient populations and the EPIDYS clinical trial and OLE? | which were in Europe. Patients were recruited before the 1st internationally published standards of care in 2009 and before the updated standards of care in 2018. Evaluating patients managed in such different health care settings before a consensus of care was established is likely to mean significant variation in standards of care across these sites with a diverse population of patients. The analyses of this dataset do not reflect more recent improvements in standards of care which in turn may impact the outcomes of patients<br><br>The UK Northstar registry is a 'live' database with ongoing recruitment of boys and young men with DMD in the UK now holding data on > 1500 patients. The study initially focused on 'paediatric' care with agreed standard monitoring and assessments in those boys managed within the 23 paediatric North star centres and subsequently extended to include > 700 adults with DMD managed within 28 adult Northstar sites.<br><br>Thus the UK registry is likely to reflect more uniform standards of care that more closely reflect UK practice than the CINRG dataset. As Northstar is a 'live' database it includes patients benefitting from more recent developments in the standards of care. However, as data collected from sites is uploaded to the database on a 'voluntary' basis with minimal additional resources, the dataset is not complete making comprehensive analysis more challenging.<br><br>For the company's appraisal, data was utilised from a more detailed analysis of adults within 3 Northstar centres with more complete datasets. Using adult data provides a 'longer' time frame to capture a range of disease milestones but does mean that some older patients may not have received the current standard of care ie did not receive corticosteroids (CS) early in the disease course as recommended in the 2009 standards of care ie were steroid naïve or did not have CS continued after loss of ambulation as recommended in the 2019 standards. This may impact the age at which particular disease milestones were achieved.<br><br>Data from the initial Northstar publications looking at median age of loss of ambulation in those treated with intermittent (12 years) and daily steroids(14.5yrs) (Ricotti 2012) feels relatively representative of what is seen in clinical practice, and the difference between the effectiveness |

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| | of the 2 regimes is consistent with that reported in the FOR-DMD study (Guglieri et al JAMA 2022)<br><br>Whilst steroid regime has been shown to impact outcome, it is also clear that individual disease trajectories vary considerable as outlined in previous sections.<br><br>Factors contributing to this include genotype and disease severity though studies looking more specifically at those within different disease trajectories have failed to identify very specific prognostic factors with conflicting results on the impact of genotype ( Muntoni et al PLoS One). Other studies highlight ethnicity and deprivation as impacting DMD outcomes and thus it becomes almost impossible to control for all potential disease variables, particularly in a rare disease where subdividing groups results in numbers too small for accurate regression analysis.<br><br>Certain publications have used propensity matching to try and improve comparisons between particular groups, in particular the Stride study, a post marketing study to look at longer term outcomes in Translarna treated patients. However, regulators have not accepted the complexity of this type of methodology<br><br>Thus, whilst simply using age at starting steroids as a comparator may appear to exclude other prognostic factors, more detailed analysis becomes increasingly complex<br><br>For example the age at diagnosis may reflect better parental/clinical awareness than more advanced disease - as evidenced by a younger age at diagnosis in Germany v UK and Canada in the FOR DMD study which did not correlate to more ‘severe’ overall disease<br><br>Age at starting steroids also reflects other factors - such as cultural acceptability of treatment. Analysing steroid regimes in natural data history datasets is further complicated by the many patients who ‘switch’ from one CS and treatment to another for different reasons and at different stages. |

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| **What is the impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints? (Sections 3.4.5, 3.4.3, 9.6 of EAR)** | In my view the predictions of outcome in the OLE group provided by the company are more representative than those in the analysis of the EAG which appear to be consistent with the age at which these milestones are reached with current recommendations of care ie daily steroid use from an early age which even in 2012 was shown to be associated with a LofA of 14.5 years. Thus added benefit from another drug which appears to further 'shift' loss of muscle power to the right - is likely to be reflected in the Lof A predicted at 17 yrs by the company's analysis of the OLE group data.<br><br>As stated above, at this point given the age of the patients it is difficult to know whether there will be a cumulative or ''fixed' benefit in terms of later milestones ie will treated and untreated patients simply show parallel declines in motor function or will there be increasing divergence with time? It is therefore impossible to say whether the age at which loss of hand to mouth function and need for ventilatory support is shifted further from the expected disease trajectory as outlined by the company or in parallel as outlined by the EAG. Either way delay in these milestones is beneficial to patients as outlined above.<br><br>Data from the non ambulant study and aging OLE population should provide further evidence about the impact on upper limb and respiratory function which in turn will allow more accurate prediction as to the age at which later disease milestones are attained. |
| **Use of 1.5% discounting (Section 4.2.5 of EAR)** | Not able to comment |
| **Overestimation of caregiver utility impact (Section 4.2.7 of EAR)**<br>This is about the company's current approach to caregiver health related quality of life.<br>Is caregiver burden expected to increase with disease severity? Would the number of caregivers be expected to increase with | Quantifying care giver health related QoL has proved extremely difficult in previous TAs looking at both DMD and SMA, both of which are progressive life limiting NM disorders.<br><br>There is no doubt that the care giver burden, on a practical level, increases as the disease advances and patients lose their independent mobility. However, attempts to apply health utility costs do not consider the emotional and social burden of carers across non mobility related disease milestones and fail to consider the additional challenges of caring for those with specific DMD complications or the impact of being a mother 'carrying' a dystrophin mutation. |

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| disease severity (i.e. between ambulatory and non-ambulatory disease states)? | On a simple level, a minimum of 1 carer can support a boy with DMD who can walk for a reasonable distance before needing support to reduce falls and or pain, or require a manual wheelchair, with at least 2 carers needing to support a boy with more severely restricted mobility who requires hoisting for transfers and help with all self care in adapted facilities.<br><br>However, many families have additional challenges that mean 2 carers are needed to manage an ambulant boy - particularly in certain situations. For example, when taking a boy with significant cognitive and behavioural issues out of the home who has no appreciation of danger and lacks insight to keep themselves and others from harm when near traffic or other hazards (stairs/steps) with poor balance and reduced exercise tolerance who cannot 'pace themselves or comply with advice to 'keep safe'.<br><br>Some mothers carrying the dystrophin mutation have associated cognitive impairment and struggle with the organisation and planning required to coordinate the multidisciplinary care for an ambulant boy with DMD and 2 carers or additional social support is required to meet the family's needs. Similarly, families with younger children or indeed other children with disabilities that may not meet the threshold for support in and of themselves, cannot effectively always support their ambulant children with DMD with only 1 carer. This is more commonly seen in those communities with high rates of genetic disease and in association with social deprivation.<br><br>In particular, the models for calculating carer utilities seem to focus exclusively on the physical support that patients need and do not consider the emotional, social and other costs of supporting a boy with DMD. The points at which carers particularly struggle do not always mirror the boy's physical ability and may be triggered by other events that bring the impact of the diagnosis into clearer focus. Diagnosis is obviously a particularly challenging time for carers as is watching their loved one lose skills and abilities and become increasingly 'excluded' from normal activities. However there are times of increased stress and anxiety - that do not reflect mobility itself - the arrival of another child, their child with DMD starting school, managing a daily medication regime in a reluctant child etc all of which can be extremely challenging for |

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| | carers who may need additional carer support to continue to meet the needs of their child. Similarly carers report the positive impact of events that might occur after loss of ambulation - academic or sporting achievements, participation in specific activities or better equipment/adaptations that reduce the pressures and 'burden of care'. In turn, this may give carers more confidence in their loved one attending school or in safely managing alone for periods allowing the carer to pursue their own 'non-caring' activities including a return to work.<br><br>A particular challenge for both carers and clinicians is the assumption that the 'burden' of caring for a young man/adult with DMD is removed by their death, as highlighted by the 'carer QALY trap'. In my experience in supporting families who have lost loved ones with DMD, many carers experience long term distress which impacts on their own mental and physical health. Sadly this has included parents whose long term relationships have broken down and some who have taken their own lives after the death of their child with DMD. In my view, it is both inaccurate and offensive to suggest that the carer quality of life 'improves' with the death of their child.<br><br>Data presented above has shown that delays disease milestones can impact quality of life and well-being ie maintaining independent ambulation, reducing need for scoliosis surgery, delaying time at which ventilatory support is required. Delays in disease progression and associated with increased survival in DMD. I am yet to meet a carer whose goal has not been to optimise the quality of life of their child and who does not have highs or lows in their well being that are not directly related to their child's mobility level and/or disease state. |
| **Costs and quality of life assumed the same in the full ventilation states and night ventilation states (Sections 4.2.7 and 4.2.8 of EAR)**<br>How would you expect costs and quality of life to compare for people who have full ventilation | The need for full ventilatory support is likely to be parallelled by a decline in fine motor and bulbar function. This in turn makes it harder for an affected patient to operate controls and function independently, such that they are likely to need increasingly close supervision and monitoring. Quality of life in these states will depend on many other factors- including access to effective technology, equipment and adaptations, ability to access and participate in chosen activities including social activities and employment and provision of reliable and skilled carers.<br><br>These issues are likely to have a greater impact on QoL than the need for daytime ventilation in and of itself. The costs of providing the necessary resources will not necessarily increase with |

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| and people who only have night ventilation? | daytime ventilatory use, though this will depend on family resources and wishes of the affected individual |
| **Overestimation by natural history model (NHM) of survival and DMD clinical progression events ( Section 4.2.6 of EAR)**<br>What percentage of people with DMD in England would be expected to survive to:<br>• age 10?<br>• age 20?<br>• age 30?<br>• age 40?<br>• age 50?<br>What would be the average age a person with DMD in England would be expected to start ventilation?<br>What would be the average age a person with DMD in England would be expected to start full-time ventilation? | Again this has been discussed in previous TA related to the management of DMD<br>There is no doubt that survival has improved over time, as evidenced in the literature, but it remains very difficult to 'predict' the life expectancy of a cohort of boys with DMD born in 2020s with those born in earlier decades<br>Published evidence demonstrates an increase in life expectancy in DMD over time with the median survival now being 30 years.<br>Whilst there are few adults with DMD surviving into their 40s and 50s now, those adults were born after steroids became an established standard of care and when access to non invasive ventilation and /or more proactive postural management was not available. Thus outcome of boys currently under the care of paediatric NM teams cannot be determined by current studies of life expectancy in adults with DMD<br>In addition the more 'unpredictable' nature of cardiac muscle involvement in DMD which though inevitable in time, can occur early in the disease course and does not follow a predictable pattern, in the way that respiratory muscle strength declines, means that some young men still die from cardiac causes in their late teens. This has an impact on overall estimates of life expectancy<br>In my view, it would be extremely unusual to see a DMD related death ( other than possible adrenal insufficiency or fat embolus syndrome) in a boy under 10 years and in a sense this would reflect a lack of appropriate acute/emergency care rather than the disease per se. I would therefore suggest survival is > 98% in those at age 10.<br>As noted there are boys who have developed significant cardiomyopathy in their teens and die as a result. However, the 2019 recommendations for care suggest that the use of cardioprotective medication is 'considered' in those > 10 years and only in the 2022 publication in the British heart Journal from the DMD Care UK project was there a recommendation for more proactive treatment with cardioprotective medication to be started before 10 years, with |

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| | the additional use of potassium sparing diuretics. Thus the potential impact on life expectancy is not yet evident.<br><br>It is now extremely unusual to start nighttime ventilatory support in boys < 18 yrs with DMD as a result of hypoventilation alone. However, sleep disordered breathing also results from obstructive sleep apnoea, more common in those with excess weight gain and a cushingoid appearance as a result of long term steroid use. Thus there are some boys with relatively good respiratory muscle strength as evidenced by an FVC > 60% who may require night time ventilation, but the numbers requiring this before 18 years of age are very small. In my experience around > 80% of patients under my care now survive until 20 years.<br><br>I find it more difficult to give an accurate figure for survival in adults as I do not have an adult case load. However, as mentioned previously, it is important to remember that published case series do not reflect improvements in current standards of care which are likely to improve life expectancy in future cohorts of patients |
| **Mismatch of HERCULES natural history model (NHM) and available randomised controlled trial (RCT) data on givinostat (Section 3.4 and Section 4.2.2 of EAR)**<br><br>This issue is about how the main outcome of EPIDYS (4SC – i.e. the mean change in the time taken to complete a standard four-stair climb between baseline and 18 months) is not an outcome built into the HERCULES model structure so | There is enough published data looking at markers of motor function in DMD to interpret changes in the time taken to perform the 4 stair climb. Studies have mapped both the minimal detectable change and minimal clinically important change in this timed functional test. The changes have been related to overall motor milestones and in particular to other timed tests used to measure functional ability in the early ambulatory phase of the disease including timed rise from the floor and the distance covered in the 6 minute walking distance test, which in turn have been shown to mirror decline in the NSAA score.<br><br>It is therefore appropriate to assume that the 4SC is a representative functional outcome measure that increases as muscle strength and power decline, in line with other accepted markers of disease progression. In addition the preservation of time take taken for 4 SC in the givinostat treated group parallels the slower decline seen in the secondary outcome measures , |

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| non-randomised evidence is used to inform treatment effects in the model.<br><br>How often is 4SC used in clinical practice settings to measure functional status?<br><br>How representative is the placebo arm of EPIDYS to NHS clinical practice? | all of which favour Givinostat with differences in NSAA score and fat accumulation in the muscle being clinically significantly in the treated and untreated groups.<br><br>There is some evidence that the 4SC is a more reproducible measure than a timed rise from the floor which has a greater interpatient and intrapatient variability.<br><br>The ability to climb steps and stairs independently is a meaningful functional outcome for those with DMD and loss of this ability occurs towards the end of the early ambulatory phase at a similar time to the loss of ability to rise from the floor independently.<br><br>4SC is not, however, routinely used in UK clinical practice as it requires a standardised set of stairs that are not readily available/cannot be easily stored in 'mixed use' outpatient clinics as they take up considerable space. Thus measurement of the 4SC is largely used as a tool in research studies.<br><br>The baseline characteristics of both the treated and placebo groups are representative of NHS clinical practice, in terms of population demographics, age at diagnosis. BMI and steroid regime. Since the publication of the FOR DMD study more NHS patients are treated with daily rather than intermittent steroid regimes and there has been a trend to increasing deflazacort use given the potentially reduced impact on weight gain and behaviour in comparison to prednisolone. In Leeds there are currently 72 patients under 18yrs with DMD. Only 2 are not on regular CS, 3 are on Vamolorone as part of the Guardian study, 43 are on daily deflazacort, 22 on daily prednisolone and 2 are on an intermittent regime which is consistent with the steroid regimes reported in the placebo group of the Epidys study. |
| **Implementation of treatment effect within the economic model (Sections 3.4, 4.2.2 and 4.2.6 of EAR)** | I do not feel qualified to comment on economic models |

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| **Are there any important issues that have been missed in EAR?** | I think I have covered the key issues in this document |

## Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Givinostat has been shown to delay decline in muscle weakness in a robust clinical trial published in a high quality peer reviewed journal and this, together with data from the initial cohort and open label extension study, has resulted in FDA, EMA and MHRA approval
The impact of givinostat is seen in addition to the benefits from corticosteroid use and is not limited by specific genotypes. Therefore benefits are potentially applicable to all those with DMD
Data from OLE studies suggest that the benefits are sustained over time, but are being further evaluated in boys with more advanced disease and younger boys in ongoing clinical trials.
Whilst the drug is generally well tolerated and as an oral drug can be administered in the home, there is a need for close safety monitoring with regular blood tests/ECGs over and above current standards of care, which will require additional NHS resources to ensure these can be completed in a timely and effective manner within NHS clinical practice.
There is continued unmet need in the management of DMD in the UK and internationally. Although Givinostat is not a curative treatment for DMD, the cumulative benefits seen in those with DMD will have a meaningful impact on quality of life and potentially life expectancy and I would strongly support its use in NHS practice for ambulant boys, with the potential to rapidly extend use to non ambulant boys pending the results of the Ulysses study.

Thank you for your time.

NICE National Institute for Health and Care Excellence

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

**Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]**

**Clinical expert statement and technical engagement response form**

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

**Please note, part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 6 May 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# Part 1: Treating Duchenne muscular dystrophy and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
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| **1. Your name** | [redacted] |
| **2. Name of organisation** | [redacted] |
| **3. Job title or position** | [redacted] |
| **4. Are you (please tick all that apply)** | ☒ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with Duchenne muscular dystrophy ?<br>☐ A specialist in the clinical evidence base for Duchenne muscular dystrophy or technology?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | Nil |
| **8. What is the main aim of treatment Duchenne muscular dystrophy?** | The main aim currently in DMD is to stop/slow progression and delay milestones, such as loss of ambulation, ventilation etc. Ultimately a cure would be the best treatment, however whilst gene therapy is promising, there are many |

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| (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | hurdles and the research and trials are ongoing, however the treatments currently with standards of care, steroids, ataluren and physio and supportive care have been our main treatment options up to date. |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | A clinically significant treatment response would be delay of these milestones, and improvement in motor milestones and quality of life, particularly in the better disease states, such as ambulatory, both early and late, transfer state and early non-ambulatory. The shifting of these milestones corresponds with later onset of ventilatory requirement in general and hence a better quality of life in the less severe disease stage.<br>If we are able to shift these milestones by 1-2 years this is clinically significant. We have already seen a shift in these milestones by increased standards of care and the use of steroids regularly in this condition, and therefore a further shift of 1-2 years would be significant along with established clinical care guidelines. |
| **10. In your view, is there an unmet need for patients and healthcare professionals in Duchenne muscular dystrophy?** | Yes, this condition is still the most severe muscular dystrophy and has no specific treatments or cure, apart from supportive treatment and steroids. Whilst Ataluren has been available for nonsense mutations (approx. 13%), it's efficacy is in question and yet none of the antisense oligonucleotide treatments (exon skipping therapies) or gene therapies are licenced in the UK. This therefore means that whilst boys with DMD are living longer due to improved standards of care, they still on average die average age 25-28 years. |
| **11. How is Duchenne muscular dystrophy currently treated in the NHS?**<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)<br>• What impact would the technology have on the current pathway of care? | Currently in the NHS when a patient is referred for a possible neuromuscular (NM) diagnosis, they are seen in the NM clinic and examined, and depending on the referral and investigations done prior to referral, the NM clinician may need to initiate investigations or already have a diagnosis on referral.<br>With DMD, many will be referred from community paediatricians or hospital paediatricians as suspected with a raised CK level and will be triaged as urgent and if genetic testing has not already been initiated, then this is requested either via the paediatrician whilst waiting for an appointment in the NM clinic or after review in the NM clinic. This is due to the fact that some paediatricians are more comfortable in discussing this with families and others would prefer this to be done in the NM clinic, where questions can be more fully answered if the paediatrician is not confident in their knowledge of DMD. |

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| | Once the diagnosis is made these children are reviewed regularly (6 monthly) in the muscle MDT clinic and initially will have more frequent appointments depending on their age and stage of DMD and the need to start treatments as soon as possible. We also have respond to the parents and their ability to cope with this diagnosis and process the information. This may mean more frequent contact and follow up by specialist nurses and psychology on the team to help them cope with this devastating news but also be able to accept the next steps in treatment and management.<br>All paediatric neuromuscular centres are signed up as Northstar sites and follow the guidelines as outlined in the 2018 (revised) DMD tripart published guidelines by Birnkrant et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018 Mar;17(3):251-267. These 3 publications outline the diagnostic pathway as well as the management from steroid initiation, monitoring, cardiac and respiratory care, bone and endocrine management, gastrointestinal and orthopaedic management as well as psychological, emergency management, transition and end of life.<br>This is generally accepted as the guideline that we follow and is regarded as an international guideline.<br>DMD care UK have more recently set up working groups specifically looking at some of these aspects and how this applies to the UK and these have also produced useful publications, many endorsed by speciality groups; cardiac and respiratory guidelines as well as endocrine guidance and steroid guidance, physiotherapy and more recently Vamorolone guidelines and monitoring. These can easily be found on their website, but follow the international 2018 guidelines. https://dmdcareuk.org/clinical-recommendations.<br>The impact of introducing the new technology, such as Givinostat, would mean that this would potentially delay the onset of milestones, such as loss of ambulation, and whilst the guidelines would still be followed including steroids (traditional or Vamorolone) and regarding monitoring and surveillance, this would |

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| | mean that the disease states would be reached at a later date and need for ventilation etc delayed. |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care?<br>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | The new medication will be used in conjunction with the current guidelines and clinical care currently delivered in the NHS, and this would be used in combination with traditional steroids or the newer dissociate steroid, Vamorolone.<br>I would expect this medication to be used in a specialist clinic where monitoring and assessments can be made as per guidelines in an MDT setting.<br>We would, if appropriate, ask the local secondary care teams to assist with monitoring in some cases, who live a distance form the specialist centre in between appointments in particular for blood tests and ECG evaluations.<br>We would inform GP's regarding the new medication and what its properties were and what potential drug interactions.<br>The investment needed would be for both coordination time and nursing time, as many centres will be using their specialist nurses to coordinate and contact families and arrange the monitoring, which will obviously take them away from other nursing role. This may need hours to be increased for these team members to enable this to be completed.<br>There will also be an increase in doctors time to both consent and counsel patients and families, as well as extra appointments for monitoring and time to review results and make dose adjustments as required. This will be in addition to the current guidelines and schedule required to ensure best level of care is given to the DMD patients. This will be more impactful at the start of the treatments and initially when starting patients on this both for those newly diagnosed and those that have been diagnosed for some time.<br>As we establish the treatment, the newly diagnosed will be started as per protocol and as part of standards of care.<br>To enable this, more nursing, coordinating and doctor hours are required and this may mean more investment for the neuromuscular teams. |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | From the evidence of the EPIDYS trial and the predictions including loss of ambulation (LOA) and rise from floor, this drug appears to shift the timelines for |

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| • Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | this neurodegenerative condition and as a result means that these boys spend longer in better disease states and more active. From the evidence we have re; LOA, the later LOA occurs the later we need to instigate ventilation and often this is impactful on scoliosis development, arm function and as a consequence quality of life.<br>As we know DMD is a continuum, and there is always a spectrum of patients that appear to do better (that is are older when they reach particular milestones) and those that do not do as well. When a child with DMD loses ambulation, we know from natural history data that these young people then have a decline in respiratory function and hence require ventilation sooner and hence more dependent on carers and are more at risk of earlier death.<br>Current health care; whilst there has been an improvement in survival with improvements in proactive care and steroid treatment, this disease is still devastating and leads to early death. A therapy that improves timelines and means that boys spend longer in the better disease states improves mental health and quality of life and whilst this will still be a shorter life, there will be improved quality. |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | This medication is a non-mutation specific therapy and therefore is appropriate for all patients with DMD, however would probably benefit those that are earlier in the disease trajectory and whose timelines can be shifted. We do not have evidence yet as to whether this drug does specifically continue work on muscles after LOA and whether it is helpful for non-ambulant patients and upper limb function however it would seem logical that it would and potentially preserve hand to mouth function, however long term data will hopefully answer this. |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?**<br>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | As this medication is an oral medication, this is easy to administer for the families as well as easy for professionals to prescribe, compared to weekly Intravenous infusions that need port access or IV lines placed each week, which is often distressing for the children/young people.<br>The practical implications are that in the initial phase blood tests will need to be arranged, but these are not difficult or expensive blood tests and clearly set out in the protocol. Platelet count and blood count to be done 2 weekly for 2 months and then at 3 months and 6 months and this is then continues with their usual |

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| | bloods per clinic appointment. Lipids and triglycerides are also monitored at 1 month, 3 months and 6 months and then as per clinic bloods.<br>The other investigation is an ECG that should be monitored when starting the drug to review QTc interval and when seen in clinic.<br>For some patients who cannot cope with regular blood tests this would not be acceptable and this will be gauged by parents and the boys themselves as to whether they will be able to cope with this.<br>For Neuromuscular teams, whilst these investigations themselves are not expensive, this does require coordination both to arrange either on site or at their local hospital and then the reviewing of results and making any changes required and subsequent testing as per protocol, so the need for extra coordination time and extra nursing time is required. |
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | As per the protocol, we would be assessing the blood counts and lipids and trigs levels as well as the ECG's and if there is any contraindication or stopping criteria is reached then they will need to stop.<br>There is clear guidance on reducing the dose of the drug twice, depending on the blood counts and lipids and trigs levels, however if there is a persistent abnormalities after reducing the dose, then discontinuation of the treatment is advised. |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | I do not think that there is any perfect way of capturing quality of life in these families and the perception of their lives.<br>The issue is that these families have not known any different and from diagnosis, live a very different life in the knowledge that their child has a life limiting condition and that they will witness them losing skills day by day, and the mental strain that has on both families and the boys themselves is immeasurable.<br>These boys are aware of their loss of skills and in particular when they losing upper limb function, or need ventilation and require more support and are less independent, they often become very anxious and have mental health issues as they are aware of their mortality. This is exacerbated if they become unwell or see their peers with DMD die. |

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| | Any treatment that can delay that deterioration is a benefit for these families and boys, and as we are aware, time spent longer in the better disease stages as described in the submitted documents from the company and as outlined in Project HERCULES is beneficial both physically and mentally for both the caregivers and the boys/young men. |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?**<br>• Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | This technology is the first to show an innovative way of improving the outcome of DMD. Givinostat is an orally active hydroxamic acid derivative and is a histone deacetylase (HDAC) inhibitor. This activity that could help to counteract the pathogenic events downstream of dystrophin deficiency.<br>Normally dystrophin is expressed in the muscle cells, in the dystrophin-glycoprotein complex (DGC) and this is key to maintaining the muscle cells membrane integrity especially after contraction, a mechanical stress. DGC also modulates chromatin dynamics and regulates HDAC2 activity. In DMD this results in increased HDAC2 activity and hence altered expression of regeneration genes. HDAC inhibitors also promote muscle regeneration and inhibit fibrosis by a direct action on fibroadipogenic progenitors and therefore promoting myogenesis. The HDAC inhibitors are also anti-inflammatory and therefore have a role in the inflammatory process seen particularly in early DMD.<br><br>As mentioned above, use of this technology would mean a shift in the timelines for DMD and is a definite unmet need in these patients. Delaying the onset of ventilation, loss of hand to mouth function, orally feeding etc improves quality of life both for the young man but also their families.<br>Delaying these milestones means that these young men, when they do lose ambulation are more skeletally mature, may not need scoliosis surgery etc |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | With this medication, whilst we monitor the bloods particularly the platelets in the first few weeks more intensely and then the lipids, once stable this should not impact too much on the boys/YP's quality of life as this is minimal and most of |

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| | these young boys/YP are used to having bloods regularly and the medication is oral so this is less impacting, compared to weekly infusions as some require. |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting?<br>• What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | Although the clinical trials use more outcome measures that are normally employed in a clinic, they do use the outcome measures that we routinely use, such as the NSAA and 10m walk/run.<br>They monitor the cardiac function and blood investigations generally that are done in clinic, in addition to more specific blood tests that during the trial showed more changes such as the lipid profile and platelet count.<br>As far as I am aware there are no adverse events that have not already been documented in the trial publications.<br>The 4SC was used in the trial and is not necessarily always done in clinic due to equipment and time constraints, but the NSAA has been used in all the natural history trials as well as routinely in clinic and in the trial and is a good measurement of stability/deterioration in children with DMD. |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | I think that the systematic review of the trial evidence is very thorough and I am not aware of any other relevant evidence that might found. |
| **22. How do data on real-world experience compare with the trial data?** | There is a number of real-world datasets including CNIRG, which is US based and also the UK dataset which is more reflective of the UK population. This has therefore been used in conjunction with the trial data, and as we are aware trial patients are homogenous in nature as they have to satisfy the inclusion and exclusion criteria, however the real-world population is more heterogeneous. |
| **23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.** | I do not think there are any equalities issues as all boys with DMD would be eligible as it is not mutation specific and would be monitored as per protocol and only if they develop side effects that would require discontinuation would this be considered.<br>As with all treatments, it will be individual, and we would need to weigh up the benefits and the potential harm for each patient and as the longer term data emerges this may give us more information as to which patient groups would benefit the most. |

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| Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this evaluation could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | In general, the earlier in a disease course the medication is started, the better the impact. Earlier in the disease course the muscle disease is not as advanced, as medications at present are targeting preserving the muscle but cannot change muscle fibres that have fibrosed and died. |

## Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

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| **Have comparators been appropriately specified in the submission? (Sections 2.1 and 2.2 of EAR)**<br>This is about the consideration of vamorolone which may displace current corticosteroid use in established clinical management following publication of NICE guidance recommending use of vamorolone in Duchenne muscular dystrophy in January 2025.<br><br>What proportion of people have vamorolone instead of standard | Givinostat is independent of steroids (traditional such as prednisolone and deflazacort) and associative steroids (such as Vamorolone).<br>Whilst the company have mentioned this in their submission, this should not be viewed as an alternative as this would be used alongside steroids, whether this be traditional steroids or Vamorolone.<br>They have a different mechanism of action and being used differently.<br>We would therefore always advocate steroid treatment as per guidelines as the evidence is strong regarding improvement in care and delaying milestones compared to steroid naïve patients and historical data, and now in addition Givinostat would be added to this to further delay milestones. |

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| corticosteroids? How would this proportion be expected to change over time?<br>What impacts whether people have vamorolone rather than standard corticosteroids?<br><br>How does the clinical effectiveness of vamorolone compare with standard corticosteroids such as prednisone? | At present we have just had the ability to prescribe Vamorolone as of the 17th April, and not many have started this yet, although I would envisage mainly the younger DMD population wanting to start this or switch, due to the beneficial effects potentially on height, bone health and possibly behavioural profile.<br>I would presume more new patients would opt for Vamorolone, rather than those that are already established on traditional steroids and this very much depends on patients/parents wishes and after we have been through the properties, side effects and the 'unknowns'.<br><br>The clinical effectiveness is very similar to traditional steroids and is as effective, the benefits are that of the side effect profile being more favourable. |
| **Definition of 'ambulant' status and implications for generalisability to UK clinical practice (Sections 2.2, 3.3.1.2, 3.3.2.2, 3.4.2.1, 3.4.2.2 of EAR)**<br>How are the following terms defined in people with DMD in NHS practice?<br>• 'ambulant'<br>• 'non-ambulant'<br>• 'late ambulant'<br>• 'early non-ambulant'<br>What clinical measures are used for ambulatory or functional status in DMD in NHS practice?<br>How do these measures differ from what may be used in clinical studies? | Generally the definitions used are as per Northstar collection forms and as used in clinical evaluation as well as the trial inclusion/exclusion criteria.<br>Ambulant: can walk 10 meters without assistance.<br>Non-ambulant: not able to walk 10 meters without assistance.<br>In general, however it is a continuum and those that are late ambulant are usually able to take a few steps but this is not particularly functional but can usually furniture cruise and get around their bedrooms, there is then a transfer state when the boys can then transfer independently from chair to bed etc and can stand with support.<br>Early non-ambulant is the stage that is usually referred as when a boy/young man becomes non-ambulant and is using his wheelchair fulltime but has excellent upper body and limb function.<br>For those patients that are ambulant, both in clinical trials and clinical follow up the NSAA is used and the 10m walk is part of that assessment as well as timed rise from the floor.<br>The 4 stair climb is an important function and demonstrates good muscle strength which is a well validated outcome measure, and used in many clinical trials in DMD and other |

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| | neuromuscular disorders and therefore was an good outcome measure for the trial but not always practical to do in a busy muscle MDT setting outside clinical trials.<br><br>The usual outcome measures and assessments done in a muscle MDT include the 10m walk and TRFF, as well as the NSAA and spirometry (FVC measurements). |
| **Post-hoc selection of givinostat OLE patients (section 3.4.2.1 of EAR)**<br>This is about the patient population used in the open label extension study (OLE). The OLE population included people who had received givinostat in the initial study ("givinostat" group), people who received placebo in EPIDYS ("delayed givinostat") and people who met the criteria for EPIDYS but were not enrolled ("naïve givinostat").<br><br>How might the efficacy of givinostat differ when excluding people who received placebo in EPIDYS ("delayed givinostat"), compared with including the full OLE population? | I think using the groups as they have done has shown that even in delayed administration, there is benefit from givinostat.<br><br>If comparing pure naïve givinostat populations with those that received givinostat (minus the delayed administration) in the initial study may give even more compelling evidence of its efficacy. |
| **Source of data to inform comparative treatment efficacy (Section 3.4.2.2 of EAR)**<br>This is about how the data used for comparative treatment efficacy | We unfortunately do not have direct comparative data for the treatment efficacy in established clinical management, however the UK registry /real-world data set would appear to be more aligned to the UK population, treatment and ages at which milestones are reached. |

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| in established clinical management may be imbalanced in prognostic factors such as baseline characteristics, type of corticosteroids and inclusion criteria for trials/registry studies compared with the givinostat clinical trial data.<br><br>Which of the following patient populations is likely to be most similar to the patient population in the EPIDYS clinical trial and OLE?<br>• UK registry study<br>• CINRG DHNS registry<br>What are the similarities and differences between these patient populations and the EPIDYS clinical trial and OLE? | As clinicians we all have our own populations and as the data shows this is a heterogenous population with some young boys requiring ventilation at aged 16 years and some not starting until they are in their early 20's. This can be mutation specific, environmental influence as well as other confounding effects which means their DMD appears to have a more severe trajectory.<br><br>The CINRG database is an older (completed 2016), mainly US based registry and whilst it is larger and more detailed than the UK registry, could be argued that it does not reflect the current state of clinical care in the UK and therefore the outcomes of the UK DMD population. It is however more extensive and has been therefore used in many publications as comparators in regard to new technologies.<br><br>The other issue is regarding steroid use and in the EPIDYS trial most boys were on deflazacort compared to prednisolone in the UK, however in the VISION DMD trial daily prednisolone was seen to be more effective than deflazacort and therefore this should not cause significant issues. This may suggest that comparing with the more recent UK registry would reflect an improved outcome from steroid use compared to those in the EPIDYS trial on deflazacort?<br><br>The CINRG registry, whilst older does have more patients on deflazacort and therefore could be argued is more aligned to the patient population in the EPIDYS as the majority of the participants were also on deflazacort. |
| **What is the impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints? (Sections 3.4.5, 3.4.3, 9.6 of EAR)** | As with any rare disease, the longer term outcomes are only going to be seen after the extension study has completed and as with many of these studies the aim is to continue treatment in these boys/YP and continued assessment and appraisal of the treatments is essential.<br><br>With rare conditions, it is not possible to have complete datasets for randomised comparisons but natural history data gives us information of what to expect and when in this condition and therefore improvement in this over time, in those that are receiving treatments, will be recorded and documented as all patients are assessed every 6 months with NSAA and PUL2 and EK2 when non-ambulant as well as spirometry and cardiac function. |

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| **Use of 1.5% discounting (Section 4.2.5 of EAR)** | Unable to answer as do not know enough about this aspect. |
| **Overestimation of caregiver utility impact (Section 4.2.7 of EAR)**<br>This is about the company's current approach to caregiver health related quality of life.<br>Is caregiver burden expected to increase with disease severity? Would the number of caregivers be expected to increase with disease severity (i.e. between ambulatory and non-ambulatory disease states)? | In DMD we would expect care giver heath and quality of life to reduce with increased burden of disease. Most parents, who are doing the caregiving and other family members, report that their own health deteriorates as the boys/young men get older and need more interventions and support. This both has a toll on the care giver physically as well as mentally and starts to limit their lives from a social perspective and their world narrows as does their sons.<br>It is often underestimated the support and needs of the care givers, as there is a general deterioration and at each disease stage, the care givers increase their level of support and continue to carry on.<br>There is a definite need for increased carers when a young person becomes non-ambulant purely from a practical perspective and the need to hoist and position and this increases as ventilation is started and then as hand to mouth function is lost and the young person becomes completely dependent. If not already introduced to other carers from agencies, this can be a struggle for these young people to adjust to, but often families rely on family members as this is more acceptable for the young person due to personal cares and intimate care is needed.<br>Often the parents, and more specifically the mum, gives up work to care for her son but this already narrows her social outlet and she becomes isolated at times. Often there are marriage break ups due to the stress involved in looking after a young person with DMD and this does put more pressure on the care giver.<br>As the young person deteriorates and needs more care input, often families have rotas to care for the young person and as they deteriorate. This means an increase in carers either from within the family and/or care agencies especially to cover night cover.<br>The fear of death is a huge psychological issue both for the young person and the carers. This exacerbates both physical health issues as well as already underlying mental health issues. |
| **Costs and quality of life assumed the same in the full** | I would expect young people who are fulltime ventilated compared to night time ventilation only to have more costs as you would expect more care giver time, whether that be a parent or an |

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| **ventilation states and night ventilation states (Sections 4.2.7 and 4.2.8 of EAR)**<br>How would you expect costs and quality of life to compare for people who have full ventilation and people who only have night ventilation? | outside agency. Most young people at this stage would need some assistance in the day re; mask and repositioning of the mask/mask straps and particularly if eating orally, they would need some assistance with feeding. Depending on level of hand function, which generally when they are 24 hour ventilated will be minimal, they need constant readjustment of arms on arm rests, noses scratched, repositioning of their legs and also hands on their controllers of their chairs. It is a constant job for a carer responding to small adjustments that need doing to keep them comfortable as well as being able to function, use their controller etc<br><br>If only night time ventilation, they often do not need as much help and support during the day and represent a better disease stage.<br><br>If they have lost hand to mouth function, this again means a different level of support and the ability to use controls and eyegaze to help with function and contact help. |
| **Overestimation by natural history model (NHM) of survival and DMD clinical progression events ( Section 4.2.6 of EAR)**<br>What percentage of people with DMD in England would be expected to survive to:<br>• age 10?<br>• age 20?<br>• age 30?<br>• age 40?<br>• age 50?<br>What would be the average age a person with DMD in England would be expected to start ventilation? | In general DMD causes gradual deterioration and whilst there have been improvements in survival; on average the age at death is 28 years, however some still die younger and others may survive for longer.<br><br>There are more adults surviving into their early 30's but it is a minority reaching their 40's and 50's (with odd case reports).<br><br>I would expect for adults that starting ventilation would be between 19-21 years and on average full time ventilation 23-25 years, although many will have an FVC <30% before this time period but many will not want to start until they feel the need to do so and this will be a gradual process with having some time on the ventilator during the day, before and after meals and before and after gaming or showering etc and this time on ventilation and the gaps in-between ventilation will gradually increase and decrease respectively.<br><br>The UK real world data used does highlight this and shows the spread of ages and whilst there are patients who have an FVC<30% they may not yet be on full time NIV at that stage even |

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| What would be the average age a person with DMD in England would be expected to start full-time ventilation? | though indicated, and as above the move from night time only to fulltime daytime ventilation, is a gradual process, with gradual increase in increments of time spent on and off the ventilator.<br>Age of death from the UK database 25.58-28.83 is accurate. |
| **Mismatch of HERCULES natural history model (NHM) and available randomised controlled trial (RCT) data on givinostat (Section 3.4 and Section 4.2.2 of EAR)**<br>This issue is about how the main outcome of EPIDYS (4SC – i.e. the mean change in the time taken to complete a standard four-stair climb between baseline and 18 months) is not an outcome built into the HERCULES model structure so non-randomised evidence is used to inform treatment effects in the model.<br><br>How often is 4SC used in clinical practice settings to measure functional status?<br><br>How representative is the placebo arm of EPIDYS to NHS clinical practice? | Timed stair tests by manual time measurement have a long-standing relevance in the assessment of patients with neuromuscular disorders in paediatrics and adults and they are able to reflect strength and function of the proximal muscles of the lower extremities, knee extensors and plantar flexors. Function tests using stair climb have excellent test-retest reliability in both, adult and paediatric cohorts. The value of combining multiple measures of function into composite prognostic scores in DMD seems feasible and looking 4SC and 10m, TRFF and 6MWD as well as NSAA together.<br><br>Practically, in a clinic setting, it is not always feasible to do this assessment as there may not be a set of standard steps as we have in trial facility available or a quiet set of stairs to take the children to, but as a functional assessment it is a reliable and easy assessment to do and for the children is not seen as perceived muscle strength testing and we can gauge how they are able to do this with hand rails needed or not as well as timing them.<br><br>The placebo group in the EPIDYS trial were following what would be the normal clinical practice apart from being seen more frequently than you would in a normal NHS clinical setting and taking a placebo. They were assessed more frequently but did not have any increased physio sessions for therapy. |

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| **Implementation of treatment effect within the economic model (Sections 3.4, 4.2.2 and 4.2.6 of EAR)** | As a clinician, I think that implementing this treatment in the early stages of the disease has the most benefit and that delaying disease progression and time spent longer in the earlier disease stages is beneficial. This may not be the case as the disease progresses and we may not be able to demonstrate physical improvement or maintenance. As with all therapies it has to be reviewed in context of the patient, its benefits and side effect profile and when the benefit is no longer outweighing the side effects then clinical decisions need to be made regarding the continuation of therapy. Whilst we cannot stop the disease process, this technology has been shown to slow this down and delay milestones and should be implemented early in the disease stage and incorporated into the clinical care guidelines. |
| **Are there any important issues that have been missed in EAR?** | No |

## Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is the first non-mutation specific disease modifying therapy that has met it's primary objectives in a clean trial.
This is an easy to administer medication and acceptable to the children and young people to take orally.
This medication delays progression of a devastating disease and hence enables young people to live longer with a better quality of life and hence has a positive effect on caregivers.
There are limited side effects and can easily be monitored and can be incorporated in the current clinical guidelines. There would be additional needs for teams to increase specialist nursing time and coordinator time to enable this; bloods and monitoring.
There are unknowns, such as length of treatment and effectiveness over time, but this is only achieved once using a drug in real time and non-trial patients. This would need investment in data collection for assessments to be recorded and analysed.

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

**Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]**

**Patient expert statement and technical engagement response form**

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

In part 1 we are asking you about living with Duchenne muscular dystrophy or caring for a patient with Duchenne muscular dystrophy. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

**You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.**

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

## Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 6 May 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# Part 1: Living with this condition or caring for a patient with Duchenne muscular dystrophy

**Table 1 About you, Duchenne muscular dystrophy in people 6 years and over, current treatments and equality**

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| **1. Your name** | [redacted] |
| **2. Are you (please tick all that apply)** | ☐ A patient with Duchenne muscular dystrophy?<br>☐ A patient with experience of the treatment being evaluated?<br>☒ A carer of a patient with Duchenne muscular dystrophy ?<br>☒ A patient organisation employee or volunteer?<br>☐ Other (please specify): |
| **3. Name of your nominating organisation** | Duchenne UK |
| **4. Has your nominating organisation provided a submission? (please tick all options that apply)** | ☐ No (please review all the questions and provide answers when possible)<br>☒ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☐ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☒ I agree with it and **will be** completing |
| **5. How did you gather the information included in your statement? (please tick all that apply)** | ☒ I am drawing from personal experience<br>☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: During the past 15 years involved in Duchenne, I have spoken to many families about living with Duchenne and heard their experiences. I attend an annual conference about |

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| | Duchenne and speak with families at those events. I am also part of several social media groups with families living with Duchenne.<br>☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference<br>☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference<br>☐ I have not completed part 2 of the statement |
| **6. What is your experience of living with Duchenne muscular dystrophy?**<br>**If you are a carer (for someone with Duchenne muscular dystrophy) please share your experience of caring for them** | I am a mum to a child who has Duchenne, my son was diagnosed shortly before his 4th birthday, he is now 19 years old. He was our only child at the time, and before he was diagnosed, we had no idea anything was wrong with him.<br>When my son was diagnosed, it was a devastating time – it was the worst news you could ever receive. The condition was so over overwhelming, especially there are so many health aspects affected, it's not just about not being able to walk when they grow older. Duchenne feels like the most severe disease there is, so many stages, so much of your body is affected by this disease. At this time, you go into a stage of grief, it feels like your whole life has been ripped away from you.<br>Knowing that they would need to use a wheelchair by the age of 10-12 years, unable to walk, take part in sports like other children of their age and live an independent life, then go on to not being able to feed themselves, and breath on their own – it's terrifying.<br>So much information was given to you at that time, so many different stages that lay ahead. It took several months to get our heads around the diagnosis, and having to look after your child at such a young age during that period of grief was incredibly hard. The wider family and friends were not able to fully support us, it felt like we were on our own trying to get to grips with what lay ahead.<br>I gave up my full-time job as attending regular hospital appointments and getting my head around everything that is needed to care for some with Duchenne, was too difficult to navigate during those first few years. This has had a negative impact on our family with regards to financial burden. |

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| | I had to go through genetic testing, realising that I was a carrier – and knowing that I wanted another child, I had to go through 3 rounds of IVF over 2 years – before finally going ahead with the egg donation route to have our second child. On top of everything, this was an incredibly difficult period.<br>During the 15 years since my son's diagnosis, I have been involved with all his care needs, which includes:<br>• Attending regular hospital appointments spanning multiple hospitals across many specialist areas - Paediatric Neurology, Bone Health and DXA Scans, Physiotherapy, Orthotics/Occupational Therapy, Wheelchair Services, Cardiac Health, Respiratory Health, Endocrine for Calcium Infusions and interventions to initiate puberty (delayed due to long-term steroid-use) and a Dietician (weight gain is a big problem with long-term steroid use, so it's important your child doesn't put on too much weight) . Keeping on top of files, ensuring latest appointments letter are retained as you will often be asked specific questions at each different hospital. As a parent, you need to become a specialist in Duchenne, which is incredibly hard to get your head around especially during the early stages, and then each stage where your son's health deteriorates – as each stage brings new challenges and choices that you need to make decisions on.<br>• Attending regular clinical trial review appointments, my son was on a Pfizer Clinical Trial for 3 years in Newcastle, where we had to attend clinic every month for an infusion. Shortly after this clinical trial was stopped (as there was no evidence the drug was working), we opted to go onto the Givinostat Clinical Trial. For this trial, we needed to attend frequent appointments in the beginning, and then regular 3-monthly appointments since the trial started and are continuing to attend appointments as we are on the Givinostat Extension Trial.<br>• Caring for someone with Duchenne is incredibly complex, it is important to advocate for your son, ensuring<br>o You are up to date with the latest standards of care. And where discrepancies exist, challenge those discrepancies – for example, |

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| | our local services in Neurology, our consultant would regularly change, and we as parents felt we knew more about our son's condition and treatment options than they did. The transitioning period from child and adult services is incredibly complex, as we transition to different hospitals and consultants – leading to delays in care being received.<br>○ You are aware/educated on all available clinical trial opportunities, weighing up the pros and cons, so that you can make informed decisions whether to put your child forward. For parents like ourselves, with limited treatment options available on the NHS, getting onto a clinical trial is your only hope of receiving a potential drug that might be delaying disease progression. You feel time if against you, and you cannot wait for approval treatments, due to how long the whole process takes. This adds extra weight on top of an already challenging condition to manage. This leads to a great deal of anxiety as you are unsure you are making the right decision at the right time for your child, and that you are up to date on what's available. You never want to miss anything, then there are tough times when you hear of other boys getting on a trial, that your son cannot access. You have the added pressure, of putting your child through various tests and extra hospital appointments, when they don't quite understand the reasons why. This leads to days off school, where they need to catch-up, so they don't get left behind in class. Sometimes these extra tests can be challenging for your child, especially so if they already have a mental health issue – such as anxiety, ADHD and autism (which is more likely for a child with Duchenne compared to the general population). But, taking part in a clinical trial is worth of all of this, especially when you know it is having a positive effect on their health and wellbeing.<br>○ You are aware of the available treatments on the NHS – mainly steroids and can weight up the pros and cons for which regime and which steroid drug to put your child on. Previously, there was a lot of |

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| | conflicting information, with different hospitals and consultants recommending different regimes. For instance, in Leicester where we live, it was advised to go on the 10 days on, 10 days off regime, but in Newcastle where they are more experienced at dealing with families living with Duchenne, it was recommended our son goes on a daily regime. Having to decide, whether your child at the age of 7 years old will prefer to walk longer in their teens whilst also having an altered physical appearance (short statue, more weight gain, cushion-gold feature, etc.) or to stay on 10 days on, 10 days off but likely to come off their feet sooner, but physically they will look more like their peers. This puts so much pressure on you making the right decision for your child, and a feeling of intense regret when they grow older and say that they would prefer to have opted for a difference choice that one you took at the time. Often your extended family will want to know the choices you make and why, it leads to a feeling of not doing enough – or question whether you are being the best parent you can be. There is also the pressure of wondering if you put your child on the right trial, and if a new trial that may be better comes along, only to find out that you can't access but you are already on a trial. All decisions that as parents you must grapple with.<br>○ You need to educate yourself on the available supplements that could help your child to support their health, such as multi-vitamins with limited evidence they work. These can also often be expensive.<br>○ You are aware what to do in an emergency (attending A&E due to an accident, illness or fall) as with long-term steroid use, they are adrenal insufficient. We have been issued with a Steriod Emergency Plan, advising that additional steroids must be given in an emergency. This means educating anyone who looks after your child – family members, friends, school, and ensuring they understand the implications of adrenal insufficiency, and feel comfortable with knowing what to do should an emergency happen. This can make |

Patient expert statement

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| | those looking after your child fearful and can result in them not being invited over for play dates or sleepovers. It also results in a lot of worry for you as a parent leaving your child in someone else's care.<br>○ They receive the right level of care and help during their schooling years, ensuring teachers are aware of their complex condition, and what care needs they need to do during school hours (physiotherapy, administering drugs in an emergency, ensuring they have access to the right equipment to be able to access school). Attending various school meetings with SENCO to keep his care needs reports up to date. Often you will need to fight to get everything your child needs and deserves. In our case, I went to my son's primary school and delivered a talk to the whole school to help educate everyone on what the condition was and how best to support Alex. In senior school, for us was the hardest time – as the younger children would point and call your child names for looking different and walking differently. At that age, all children want to do it fit in and be like their peers. We had a difficult time, getting school to find alternative sports that Alex could take part in, we knew it was important to keep active – and often we would find out that he was just sitting on the side lines watching whilst his friends would take part. He would also miss out on class, when he was too tired to walk the distances at the end of the day.<br>○ To recruit external carers as and when needed to help support your family, especially during the later stages of the disease, when you need to keep a close eye on your son if he is on a ventilator. Often parents will say how they will not get a good night's sleep because they need to turn their sons over several times throughout the night. It is not always possible to do all the care by yourself, especially if you must work and look after other family members. Often, I hear of families being let down by their carers frequently, leading to stress |

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| | and anxiety of not being to go to work or feeling too tired to do anything.<br>○ They are offered support with mental health, often not something which your neurology consultant will discuss with you. It's important to spot any signs that you child needs this help and act accordingly. This can be challenging, especially during teenage years when they don't talk to you. So, you need to educate school for things to look out for and ask friends' parents to keep an eye on this too.<br>• Ensuring your family and child receives the available financial help and support – including completing Disability Living Allowance forms, and Carers Allowance. Often these will be challenged, so you will need to fight for what your child deserves. This is a lengthy, complex and challenging process – leading to a feeling of drowning in forms and trying to navigate the system. As parents, it's important we can speak with others going through the same ordeal – luckily because of social media we are in lots of family groups where parents looking after a child with Duchenne can ask questions and seek support – a lifeline for families like ours. Luckily, our local Care Advisor was able to provide lots of advice and support, especially so when we were rejected the higher level of disability allowance.<br>• Manage the process of home adaptations, researching and applying for grants to support this work is incredibly difficult and time consuming. For ourselves, we needed to move home as it wasn't suitable for adapting to meet his changing needs (both now and in the future) and had to move to a completely different area as there were limited bungalows available where we lived. Once we had moved home, it was important for us to be prepared for when our son would not be able to walk many years before this happened. With Duchenne, you never know when the next step of decline will happen, so you must prepare – even though it is heart-breaking and difficult to do. We had to move away from our son's friends, which was hard for him personally – especially as making new friends with Duchenne can be extra hard. Even thinking about putting in ceiling railings to support future |

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| | additions with ceiling hoists – the last thing you want is for your child to be staring at this equipment, as it's a sign of things to come. At the same time, if you don't forward plan – and you need it – you need it then and cannot wait.<br>• Ensuring your child has the right equipment needed to support their day-to-day activities and lifestyle choices, including wheelchairs (manual and power chairs), football wheelchairs, night and day splints, hoists and standing frames. Often you will need to apply for external grants or fundraise yourself to support the costs as they are highly expensive and often not available on the NHS. This has been the case for us, where we applied for several grants for a manual wheelchair and battery powered device which costed £10K, and a standing frame costing £2K, which we paid for personally. We have been told that we must apply for a powered wheelchair – ahead of when we need it – as it can take several months to get one through the NHS. Our son is not keen on equipment in the home he doesn't yet need – as it's a reminder of what's to come. We must navigate this process, whilst keeping our son's mental health in check.<br>• Travel, holidays and breaks must be meticulously planned and carefully considered ensuring that the mode of transport, accommodation and facilities are suitable. Often you will arrive at your destination, and the disables toilet they had promised, isn't as accessible as you need it to be. This is same for booking a restaurant or any activity away from home. It can place a lot of frustration and disappointment on the whole family, and friends – as you must cancel trips or leave early because the facilities are not as promised.<br>• Attend annual Duchenne related conferences in the UK, to keep abreast of medical advances, clinical trial opportunities, improvements in care standards and to speak with other parents who have a child with Duchenne.<br><br>Alex will often say he feels like an old man – with his aches and stiff joints and muscles. There is not a single day that goes by when you worry about your child, it |

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| | might be that they can't do the things they want to do with their friends, or they don't get invited along – as they will struggle to keep pace. Or it could be that they feel fatigued and unable to do what they had planned for that day and get upset. Often a child with Duchenne will get angry at parents, because they need to take it out on someone. You feel helpless sometimes and wish you could take the condition away. It's a constant battle to keep positive, upbeat and support your child when they need it most. It is relentless, even holidays are a time when you notice even more your child is struggling – there is never a day off from the worry and concern and this places a huge amount of stress and anxiety on family members.<br><br>Alex has been admitted to A&E on two separate occasions, once when he was 9 years old as he broke his hip – he stood on a cricket ball whilst playing cricket and did the splits as his muscles were too weak to stop the break. He had to be operated on, and back on his feet as quickly as possible to prevent further muscle loss that would not be regained. Then last Summer, when he was admitted with diarrhoea and had to stay in hospital for 5 days as they didn't know what was wrong with him – this stay resulted in Alex coming off his and is now 100% wheelchair dependent. It was especially hard, as he could no longer go on a planned holiday, which we had planned meticulously for him. This was a big blow when he had just turned 18 years old. The problem with Duchenne is you are always trying to second guess when the next stage will happen, and forward planning is very hard. It often leads to disappointment, and this is very hard on mental wellbeing for your son and the whole family.<br><br>All you want for your child is to enjoy the things their friends are doing, but with Duchenne you are constantly having to think of different things to do with them that they can access and take part in. Keeping them mentally healthy is a priority, whilst trying to look after yourself and the rest of your family is hard.<br><br>As a family, we decided to set up a charity to raise awareness and raise funds to pay for medical research – we find this keeps us positive and actively engaged in |

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| | making a difference for the future outcome of this disease. As a parent living with a child with Duchenne – you find that hope is so important, hope that better treatments are going to come along to help extend their life and their quality of life. |
| **7a. What do you think of the current treatments and care available for Duchenne muscular dystrophy on the NHS?**<br>**7b. How do your views on these current treatments compare to those of other people that you may be aware of?** | There is a **distant lack of treatment options available** on the NHS for Duchenne. Duchenne still has a **high unmet medical need**. Steroids are the only current option, and these come with many significant negative side effects. At best, they delay your child from going into a wheelchair for a few years at best. There is nothing at present that has been approved that has been approved that will delay disease progression for longer. Families are desperate for more treatment options that will help their child live a longer and enjoy a more fulfilled life.<br>With regards to care standards, these are improving now that charities like Duchenne UK have developed and published care standards that are relevant in the UK. They help parents like us to advocate for your child in the area you live in. They give you the power of knowledge of knowing what the best standards of care for your child is, and how to access them.<br>As far as I am aware, and I am on various social media family groups, whilst also knowing personally families affected by Duchenne and running a charity focussed on bringing more effective treatments to market – that this view is the view taken by others. There is a **distinct lack of treatments available** on the NHS for those living with Duchenne. |
| **8. If there are disadvantages for patients of current NHS treatments for Duchenne muscular dystrophy (for example, how they are given or taken, side effects of treatment, and any others) please describe these** | Steroids have many devastating side effects – such as delayed puberty, weight gain, cushion gold features, weakened bones, stomach issues, mood swings, anger issues, shortened height - leading to boys looking very different than their peers (also leads to poor mental health) and adrenal insufficiency. Also, for parents they must make difficult choices on the regime and type of steroid to take, weighing up the pros and cons. Often boys will <u>not</u> benefit from steroids, as they decide to come off them because of the negative side effects are too much to bear/outweigh the benefits. Steroids are unlikely to help much as the disease progresses. My son has been on steroids since the age of 4 years, and we witnessed severe mood swings, weight gain, cushion gold features and a fracture – but decided the benefits out weighted the negatives. |

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| **9a. If there are advantages of givinostat over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?**<br>**9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**<br>**9c. Does givinostat help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** | **9a**. My son has been taking part in the Givinostat Clinical Trial for 6 years (started January 2019), and during those years he continued to walk beyond the years we believe he would have done, without taking this drug. He only stopped walking and now using a full-time wheelchair at the age of 18 – this is rare for a boy with Duchenne. He is however able to stand and self-transfer due to his good upper body strength. I truly believe that Givinostat has helped to delay disease progression as he is doing so well for a young man living with Duchenne, and the benefits are huge:<br>• **Good health** – my son's cardiac and respiratory health is excellent, I strongly believe this is because he's been able to stay upright and mobile throughout his teenager years. Being able to stand, self-transfer and self-propel also helps keep him fit and healthy. He does not suffer with any spinal deformities, possibly because he's continued to walk for so long. He was able to reach his full growth potential before he came off his feet at 18 years old, which has kept his bone density within normal range. This has given him time to build a great friendship group, which is so important for a teenager navigating this path into adulthood and is a good ground for his future years as an adult. He is now wheelchair dependent, but still able to self-transfer and self-propel, which gives him so much freedom and independence. Not only does this improve his and our quality of life, but it also keeps him positive and mentally strong.<br>• **Quality of life** – this drug has helped improve quality of life on a grand scale, because our son has enjoyed additional years being able to stay mobile and, on his feet, walking up to the age of 18 years old. Being able to take part in daily activities without the use of a wheelchair, kept him independent and continue to access most activities during his school years. He has been able to socialise with friends and his younger sister during those important teenager years, where he has built up personal confidence. He's been able to take part in many activities during this time, that he would not have done had he been in a wheelchair including enjoying theme parks and water parks with friends and family, a zipwire challenge, light aircraft flying lessons, and taking part in outdoor activities with Scouts, plus many |

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| | more. My son was able to take his driving lessons whilst still walking and was able to enjoy driving a non-adapted car – much like his peers. This was always a dream for him. These have led to incredible personal experiences; he would not have otherwise had the chance to do leading to improved mental wellbeing and giving him hope for a better future. This has also had a positive effect on the whole family, knowing that he has enjoyed life to the max during these important teenager years. Taking Givinostat has given us all so much hope for the future. Even after he came off his feet, he is still able to have a great quality of life – as he can self-propel in his wheelchair, now drives a non-adapted car – so he can come and go freely – take himself to university, work and socialise with friends. He has strong upper body, and this continues to see him live a relatively independent life. He's even started seeing a girl, which is something we never thought would happen – I cannot put a price on this, it is so important for him to live a relatively normal life.<br>• **Self-care** – by being able to walk for longer, he has – and is still – able to take care of himself without much support from others when it comes to washing himself, getting dressed, self-transferring from his wheelchair to a shower chair, going to the toilet, feeding himself, accessing his computer, being able to self-propel in a manual wheelchair so that he can freely get around the home and garden, being able to wheel himself to his car, accessing the fridge and cupboards so that he can help himself to food and drink. This is incredibly important to him, and still at 19 years old – he can do all these things. It has had a huge impact on the wider family, knowing that he is independent and able to look after his personal self-care. This has led him to become a confident, and able young man who is positive, happy and full of ambition for his future working and gaining a degree at university. He's now doing an Apprenticeship Degree. Knowing that Alex can be left at home alone for short periods of time, as he is able to quickly get out of the house should there be a fire at home – gives him and the whole family a better quality of life as we are able to go out without him, giving him more independence. |

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| | **9b.** Whilst all the above are extremely important, I feel the most important of all, is the positive impact on quality of life. When my son was first diagnosed, the grief felt was of him not being able to achieve what he wanted too during his younger years. It cannot be underestimated how important it is for a teenager to be able to live independently, they are the foundation years to build a great life ahead for yourself and those around you.<br>**9c**. It is still the intention that steroids are offered alongside Givinostat, and this has been the case with our son. So unfortunately, we cannot say that Givinostat will overcome all these disadvantages – although being more active helps with weight gain, bone density, less likely to be affected by scoliosis and cardiac health as you are more active for longer. Also, it is thought that Givinostat also improves upper body strength. It might be in the future, with the introduction of Vamorolone that fewer side effects will be experienced. |
| **10. If there are disadvantages of givinostat over current treatments on the NHS please describe these.**<br>For example, are there any risks with givinostat ? If you are concerned about any potential side effects you have heard about, please describe them and explain why | There are some side effects with Givinostat, however personally we have not experienced anything untoward, and certainly none that means it is a disadvantage over current treatments on the NHS.<br>Twice during the past 6 years, has Alex's blood count need to be double checked as Newcastle had raised concerns following a trial review appointment. But on both occasions, the second blood test has not flagged anything untoward. This was just a minor inconvenience for us arranging the repeated blood tests in hospital.<br>Being on a clinical trial, also means your son is regularly reviewed in clinic – this is a benefit, as you can discuss any concerns with your consultant more regularly than if you are not on a clinical trial. |
| **11. Are there any groups of patients who might benefit more from givinostat or any who may benefit less? If so, please describe them and explain why**<br>Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | No, I believe all children and young adults living with Duchenne will benefit from taking Givinostat. As it works to help delay disease progression overall, including upper body function (a crucial part to help caring for yourself, and taking part in activities, including working, being able to access your joystick on your wheelchair, typing, eating and hugging your loved one). Delaying disease progression will help with overall health – including cardiac and respiratory health – and improved mental health of the patient and their family members. It should be made available to |

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| | everyone, including those who are no longer able to walk and for boys as well as girls affected by this disease. |
| **12. Are there any potential equality issues that should be taken into account when considering Duchenne muscular dystrophy and givinostat? Please explain if you think any groups of people with this condition are particularly disadvantaged**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here. | No there are no equality issues, this drug should be made available to everyone. |
| **13. Are there any other issues that you would like the committee to consider?** | The impact of carers and family members' quality of life. This disease does not just affect the person living with Duchenne, but everyone who cares for them. This condition affects the family on a huge scale, impacting their quality of life – and mental health – and their ability to continue contributing to society, living a good life and being able to look after others at the same time (parents, siblings – as well as caring for themselves). |

# Part 2: Technical engagement questions for patient experts

## Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

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| **Have comparators been appropriately specified in the submission? (Sections 2.1 and 2.2 of EAR)**<br>This is about the consideration of vamorolone which may displace current corticosteroid use in established clinical management following publication of NICE guidance recommending use of vamorolone in Duchenne muscular dystrophy in January 2025.<br><br>What proportion of people have vamorolone instead of standard corticosteroids? How would this proportion be expected to change over time?<br>What impacts whether people have vamorolone rather than standard corticosteroids? | Initially the uptake of Vamorolone may be small, as it is likely that the majority of take up will be from the steroid naïve patients will opt for this choice as opposed to other steroids offered to them, because of the lesser side effects.<br><br>It is a bigger decision to later switch over to Vamorolone as it is unknown whether the benefits will out weight any risks, there is also the consideration of adrenal insufficiency. For the older boys, where height cannot be reversed, therefore there is less benefit to switching over to Vamorolone.<br><br>It is likely the proportion of children taking Vamorolone over time will increase, as we learn more about the benefits over the longer-term. Also, if we expect most newly diagnosed families |

Patient expert statement

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| How does the clinical effectiveness of vamorolone compare with standard corticosteroids such as prednisone? | will opt for this choice over other steroid choices, it will likely become the mainstay over the following years. It is all about choice of what families believe to be important to them and their child, in terms of side effects and benefits.<br><br>The impacts of Vamorolone over standards steroids is improved height and growth and improve bone health and density.<br><br>The clinical effectiveness of Vamorolone compared to other steroids, are it is still early days to say whether muscle function will improve with this drug over time compared to other steroids. However, the clinical effectiveness will be on lesser side effects – stunted growth is a major concern amongst boys living with Duchenne. You look different and younger to your peers, and this has a huge negative emotion for them and likely to impact quality of life. Also, bone health is vital for boys living with Duchenne, and it is likely Vamorolone will improve bone health.<br><br>It is unlikely we will switch over, because our son is now 19 years old and will not benefit it not stunting your growth, and we cannot be sure the Vamorolone's benefits will outweigh our current regime. As our son is doing well, we would not want to hinder anything that we currently doing. |
| **Definition of 'ambulant' status and implications for generalisability to UK clinical practice (Sections 2.2, 3.3.1.2, 3.3.2.2, 3.4.2.1, 3.4.2.2 of EAR)**<br>How are the following terms defined in people with DMD in NHS practice? | Ambulant – can still walk/stand independently without a wheelchair or walking aid. Likely still to need a wheelchair for longer distances or periods of fatigue/having a bad day. This can also be the case, when your child has been very active one day, the next day they may need to rest and use a |

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| • ‘ambulant’<br>• ‘non-ambulant’<br>• ‘late ambulant’<br>• ‘early non-ambulant’<br>What clinical measures are used for ambulatory or functional status in DMD in NHS practice?<br>How do these measures differ from what may be used in clinical studies? | wheelchair. For our son, he was ambulant until the age of 18 years old – although he was having longer periods of needing to use his wheelchair, especially when on family holidays and we were doing lots of outdoor activities. Children/young adults are also likely to need a wheelchair to get from A to B – so they can enjoy the activities when they arrive, this helps with energy levels and their enjoyment experienced whilst taking part in activities. It also prevents them from failing and hurting themselves, if they are tired. Gives you more flexibility and peace of mind to get out and enjoy activities. By using a wheelchair sometimes, you can go faster and further – as a child with Duchenne walks at a very slow pace.<br><br>Non-ambulant – unable to walk independently, requires a wheelchair to get around. Might still be able to self-transfer and stand so they can move from a wheelchair to a chair, toilet seat, shower chair, car seat – certainly in the early non-ambulant stages. This is currently the case with our son, he uses a wheelchair all the time now and is unable to walk – but can stand for short periods of time and is able to self-propel short distances and can self-transfer. This is because his upper arm function is still strong.<br><br>Late-ambulant – still able to walk short distances (or in the home environment, but not outside), but unable to walk longer distances without the use of a medical device such as a wheelchair or scooter. They have limitations with muscle fatigue and will require periods of rests when walking short distances. They are likely to experience falls due to being unstable on their feet and experiencing fatigue. |

Patient expert statement

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| | Early non-ambulant – unable to walk, requires a wheelchair to get around, but is still able to stand/self-transfer from a wheelchair to a chair/car seat/toilet/bed.<br><br>With Duchenne, you may have good days and bad days – it all depends on what you did the previous day/week. If my son has had a busy time at school, he might want to use his wheelchair for a few days until he feels strong enough and safe enough to continue walking. We are always told to use a wheelchair to help preserve energy levels and to avoid falls. The transition from walking to not walking can take several years, and there is no specific day that you recall where it happens. It's a slow and gradual process most of the time. And this is a good thing, as it allows both the child/young adult and family to get used to using a wheelchair.<br><br>Being able to stand and self-transfer is so important, as you are still then able to live a relatively independent life. You need upper body strength to do this, and it is likely Givinostat will support this for much longer than without it. |
| **Post-hoc selection of givinostat OLE patients (section 3.4.2.1 of EAR)**<br>This is about the patient population used in the open label extension study (OLE). The OLE population included people who had received givinostat in the initial study ("givinostat" group), people who received placebo in EPIDYS ("delayed givinostat") and people who met the criteria for EPIDYS but were not enrolled ("naïve givinostat"). | I support the charity's response. |

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| How might the efficacy of givinostat differ when excluding people who received placebo in EPIDYS ("delayed givinostat"), compared with including the full OLE population? | |
| **Source of data to inform comparative treatment efficacy (Section 3.4.2.2 of EAR)**<br>This is about how the data used for comparative treatment efficacy in established clinical management may be imbalanced in prognostic factors such as baseline characteristics, type of corticosteroids and inclusion criteria for trials/registry studies compared with the givinostat clinical trial data.<br><br>Which of the following patient populations is likely to be most similar to the patient population in the EPIDYS clinical trial and OLE?<br>• UK registry study<br>• CINRG DHNS registry<br>What are the similarities and differences between these patient populations and the EPIDYS clinical trial and OLE? | I support the charity's response. |
| **What is the impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints? (Sections 3.4.5, 3.4.3, 9.6 of EAR)** | I support the charity's response. |
| **Use of 1.5% discounting (Section 4.2.5 of EAR)** | I support the charity's response. |
| **Overestimation of caregiver utility impact (Section 4.2.7 of EAR)**<br>This is about the company's current approach to caregiver health related quality of life.<br>Is caregiver burden expected to increase with disease severity? Would the number of caregivers be expected to increase with disease severity (i.e. between ambulatory and non-ambulatory disease states)? | I support the charity's response.<br>From the point of diagnosis, both parents (and extended family and siblings) are significantly impacted due to the complexity of this disease. Your mental health, and overall wellbeing is severely affected as you navigate what this disease means for your child and your family. |

Patient expert statement

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| | Whilst one family member like me may do most of the caring, the burden is affected by everyone close to them. They all worry and are concerned by the family member affected by Duchenne. You all experience the problems they face – both in terms of health, independence – but their mental health and wellbeing. Grandparents, uncles and aunties and cousins, as are close friends all affected.<br><br>You experience grief and loss at the diagnosis stage, and then at each stage of loss of health state. Early non-ambulation is a key point when you experience a loss of your child not being able to do what they used to do. The level of care and worry vastly increases during this time. Also, your child will become increasingly worried and anxious as the grow up, as they understand more about what the condition is, and what lies ahead for them.<br><br>Whilst we are not yet at this stage, the most difficult time for any family is when your child loses their ability to use their arms. This is when care increases greatly. You then need to do everything for them, including supporting them with going to the toilet, bathing, transferring them from wheelchair to bed, etc. For families, it is worrying about the next stage of decline that always plays on your mind, trying to foresee when/what will happen what is needed and how this is going to affect your child and the whole family. Often the thought of the next stage is worse, than when it happens.<br><br>As the disease increases, the time you need to support your child increases severely. Especially, so when they are using ventilation, as you care for your child overnight. |

Patient expert statement

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| | You are likely to then need to external support from additional carers to look after your child, as it's not possible to do everything yourselves – especially having to look after other family members and work and earn money to pay bills and to live. This is likely to be overnight support and help.<br><br>I have spoken to many families who have sadly lost their child, and you never get over losing them. The sadness affects your day life, as all the fears you had when they were diagnosed and growing up have come true. As parents, you will literally due anything to keep your child alive, no matter how difficult it is caring for them. They mean the absolute world to you. There is no way life can ever return to normal, and certainly never back to pre-diagnosis state. Quality of life is vastly affected when you have lost your child, regardless of the age they are taken away from you.<br><br>I often lay awake at night worrying that my child is okay, not just from a health perspective, but from a wellbeing perspective, they don't always tell you things. They tend to hide how they really feel to protect their loved ones. That's one of the hardest things to deal with. The physical aspects you can manage, it's hard work – but you can get through this. It's their mental wellbeing that's the hardest. All you want is for them to be happy, and to enjoy life – and feel that they belong in a society that doesn't always understand them.<br><br>You often feel guilty for giving this condition to them, but also because you can't take it away. You feel guilty that you are normal, and they struggle with everyday life. |

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| **Costs and quality of life assumed the same in the full ventilation states and night ventilation states (Sections 4.2.7 and 4.2.8 of EAR)**<br>How would you expect costs and quality of life to compare for people who have full ventilation and people who only have night ventilation? | I expect the level of care to increase with night ventilation, as it is impossible to stay awake or be woken up several times during the night to ensure they are safe and breathing and that the machines are working correctly – and then to carry on caring and living your life throughout the day.<br>I expect you will need external paid-for carers to support you throughout the night. Also, if you are working you will need support throughout the day. |
| **Overestimation by natural history model (NHM) of survival and DMD clinical progression events ( Section 4.2.6 of EAR)**<br>What percentage of people with DMD in England would be expected to survive to:<br>• age 10?<br>• age 20?<br>• age 30?<br>• age 40?<br>• age 50?<br>What would be the average age a person with DMD in England would be expected to start ventilation?<br>What would be the average age a person with DMD in England would be expected to start full-time ventilation? | I agree with the charity's response. |
| **Mismatch of HERCULES natural history model (NHM) and available randomised controlled trial (RCT) data on givinostat (Section 3.4 and Section 4.2.2 of EAR)**<br>This issue is about how the main outcome of EPIDYS (4SC – i.e. the mean change in the time taken to complete a standard four-stair climb between baseline and 18 months) is not an outcome built into | I agree with the charity's response. |

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| the HERCULES model structure so non-randomised evidence is used to inform treatment effects in the model.<br><br>How often is 4SC used in clinical practice settings to measure functional status?<br><br>How representative is the placebo arm of EPIDYS to NHS clinical practice? | |
| **Implementation of treatment effect within the economic model (Sections 3.4, 4.2.2 and 4.2.6 of EAR)** | I agree with the charity's response. |
| **Are there any important issues that have been missed in EAR?** | I agree with the charity's response. |

## Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is an unmet medical need with very limited treatment options for Duchenne.
- Living independently in teenager years, being able to walk/stand equates to vast improvements in QOL.
- Mental wellbeing of patients and family is incredibly important, especially impacted by being able to live independently for longer.
- Overall health is vital in living a good quality of life, including bone, respiratory, digestion and cardiac health.
- Having hope for a better future is critically important for children and young men living with Duchenne, and their families.

Thank you for your time.

Patient expert statement

NICE National Institute for Health and Care Excellence

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

**Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]**

**Patient expert statement and technical engagement response form**

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

In part 1 we are asking you about living with Duchenne muscular dystrophy or caring for a patient with Duchenne muscular dystrophy. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

**You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.**

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

## Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 6 May 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# Part 1: Living with this condition or caring for a patient with Duchenne muscular dystrophy

**Table 1 About you, Duchenne muscular dystrophy in people 6 years and over, current treatments and equality**

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| **1. Your name** | [redacted] |
| **2. Are you (please tick all that apply)** | ☐ A patient with Duchenne muscular dystrophy?<br>☒ A patient with experience of the treatment being evaluated?<br>☒ A carer of a patient with Duchenne muscular dystrophy ?<br>☐ A patient organisation employee or volunteer?<br>☐ Other (please specify): |
| **3. Name of your nominating organisation** | MDUK and DUK |
| **4. Has your nominating organisation provided a submission? (please tick all options that apply)** | ☐ No (please review all the questions and provide answers when possible)<br>☐ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☐ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☒ I agree with it and **will be** completing |
| **5. How did you gather the information included in your statement? (please tick all that apply)** | ☒ I am drawing from personal experience<br>☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:<br>☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference |

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| | ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference<br>☐ I have not completed part 2 of the statement |
| **6. What is your experience of living with Duchenne muscular dystrophy?**<br>**If you are a carer (for someone with Duchenne muscular dystrophy) please share your experience of caring for them** | [redacted]<br>I was diagnosed with Duchenne Muscular Dystrophy when I was three years old.<br>I don't remember anything about my diagnosis, but I know it was upsetting for my family, and they worried about my future.<br>Since my diagnosis, my friends and family have campaigned tirelessly to fund research into finding a treatment for Duchenne. I can never thank people enough for everything they have done to help me and the Duchenne community.<br>In my short life, I have already taken part in three tough clinical trials. The first two trials failed dramatically, which was heartbreaking for me and my family.<br>Clinical trials are very hard to take part in. You have to give your blood, sweat and tears to take part.<br>What I want to tell you about in this written submission is about the clinical trial that I am on now for Givinostat. A drug |

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| | that has been licensed by the MHRA for everyone over 6 living with Duchenne.<br><br>The black and white results of the data show the drug is slowing down the progression of the disease, but I would like to add some colour to that data by sharing my story with you.<br><br>I started the treatment when I was 12 years old - an age at which boys with Duchenne typically can stop walking. I don't remember much about the start of the clinical trial other than the drug tasted bitter and I went a bit picky with the foods I liked. I didn't want prawn cocktail!<br><br>I did have a platelet count drop which meant we had to watch for bruising, which I never got. My bloods are now fine, and I am back to enjoying a prawn cocktail.<br><br>I never noticed any major improvements when I started taking the drug, but the remarkable thing was, at 12, I stabilised and seemed to stay the same for four years.<br><br>This meant whilst my Duchenne friends were losing ambulation, I was still able to walk around high school, get my own food from the canteen, hang out with my friends anywhere (steps weren't a problem), go to my friends' houses for |

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| | sleepovers (I didn't worry about access) and go on residential school trips without anyone needing to do my personal care.<br><br>I managed to continue walking until I was 16 years old and can still transfer and stand at 17 years old in a standing frame.<br><br>At 16 I went through a difficult time at school with bullying that really impacted my mental health. In one incident I was picked up in my manual wheelchair and put at the top of a set of steps so I couldn't get down.<br><br>During that time due to the pressure I was under, in frustration accidently flipped my manual wheelchair (which had no tippers) which led me to me breaking my arm and shoulder. My bones are weaker because I take steroids so they break more easily.<br><br>The impact of fractures meant I struggled to balance to walk and felt safer staying in my power wheelchair. I stopped using my manual wheelchair in school. You can't pick someone up with the weight of a powerchair.<br><br>It wasn't muscle weakness that took me off my feet but the emotional impact of Duchenne. I will always wonder if I didn't have that accident would I still be walking? |

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| | I picked myself up though a good support network and continued with my education.<br><br>Despite a difficult year 11 at high school I passed my GCSEs and managed to get a place at college doing a BTEC Level 3 in Graphic design.<br><br>Unlike my friends with Duchenne, I have never had to have a reduced timetable due to tiredness. I have stayed full time in high school and college.<br><br>At college and home, I manage all my toileting needs. I do not require any help as I can transfer myself. This gives me dignity and privacy.<br><br>I can transfer from my bed to my wheelchair myself which reduces the burden of caring for me for my parents. People don't have to get up in the night to take me to the toilet. This means my parents are not as tired and can both hold down fulltime jobs.<br><br>I do seem to have very good energy levels, and I need them because it does take a lot to manage my condition. I have to manage lots of medications and appointments. I am lucky that I |

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| | do receive the standards of care recommended by the DMD Care UK project.<br><br>I can independently catch the bus from college to home which gives me a lot of freedom. I do always have to plan my journeys so I don't encounter steps but I am able to go out independently. I am lucky that I can still self-propel in my manual wheelchair as it makes a lot of places and vehicles more accessible than when I am in a power wheelchair.<br><br>Being able to get out and about independently means I can get out and mix with other people and make and maintain friendships. I like to meet my friends and girlfriend to go to the cinema, shopping and Nandos.<br><br>I noticed I don't get sick with bugs like my Duchenne friends and I have never been hospitalised with illness which is common for people with Duchenne due to them having a weaker respiratory system.<br>I do believe I have stayed well and had the stamina to do so well because I am taking Givinostat. |

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| | My greatest passion in life is wheelchair sports. I play power hockey and powerchair football. I do this on top of full-time college, I train twice a week and play on a weekend.<br><br>My wish is to stay on this drug so I can achieve my dreams of representing England in powersports and I want to go to university to study graphic design. I have even looked at doing an apprenticeship with the BBC.<br><br>Through playing powersports, I have made many friends with Duchenne. I have watched them deteriorate over the past four years while I stayed pretty much the same.<br><br>I am still able to transfer independently. I need a lot less help than my friends who are the same age as me or younger.<br><br>I have watched as my friends with Duchenne need help having drinks lifted and food cut up. I don't have these problems. It breaks my heart to see them struggling. I am able to make myself snacks and drinks and they can't do that.<br><br>I watched my friend having to have his top taken off at training by his carer because he was too hot. I don't ever have to ask for help change a top or outfit. I can brush my teeth and brush my hair myself. I able to manage my own appearance. |

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| | My friends at powerhockey watch me independently transfer while they are hoisted, and it has felt unfair that they can't have the same treatment as me so they too can achieve their dreams.<br><br>At times I did feel judged by them because I was the boy that got the drug and they didn't.<br><br>I am glad givinostat is approved by the MHRA for ambulant and non-ambulant boys with no age restrictions in place. I want NICE to give my friends the chance that I got almost 5 years ago to access a treatment that is now proven to slow the progression of the disease.<br><br>Thank you to everyone that has supported me on my journey to find a treatment for Duchenne. |
| **7a. What do you think of the current treatments and care available for Duchenne muscular dystrophy on the NHS?**<br>**7b. How do your views on these current treatments compare to those of other people that you may be aware of?** | **There are limited effective treatment options. We need more options.**<br>**I follow the care recommendations made by DMD Care UK.**<br>**The recommendations can be viewed here.**<br>**DMD Care UK**<br>**Daily, I take steroids, 3 types of heart medication to protect my heart and vitamin D.**<br>**Every 6 months I have a bisphosphonate infusion to help strengthen my bones.**<br>**Once a month I have a testosterone injection.** |

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| | **Care can be delivered differently across the country due to how individual services are funded. DMD Care UK aims to try and reduce that disparity.** |
| **8. If there are disadvantages for patients of current NHS treatments for Duchenne muscular dystrophy (for example, how they are given or taken, side effects of treatment, and any others) please describe these** | Steroids have horrendous side effects. Some of the side effects are that they can increase your appetite leading to weight gain, stunt your growth, stop puberty, weaken your bones increasing your risk of painful fractures that can cause a loss of ambulation, cause cataracts and can negatively affect your behaviour. |
| **9a. If there are advantages of givinostat over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?**<br>**9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**<br>**9c. Does givinostat help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** | **a) See above statement in question 6.**<br>**b) Givinostat gives me the strength to have independence to live my best life and is helping me achieve my goals.**<br>**c) I walked for longer by taking Givinostat. Steroids reduce bone density. By walking longer your bone density stays higher so you have less risk of fractures that can end ambulation.** |
| **10. If there are disadvantages of givinostat over current treatments on the NHS please describe these.**<br>For example, are there any risks with givinostat ? If you are concerned about any potential side effects you have heard about, please describe them and explain why | See above statement in question 6.<br>All the side effects were managed and resolved within 6 months. |
| **11. Are there any groups of patients who might benefit more from givinostat or any who may benefit less? If so, please describe them and explain why**<br>Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | Everyone living with Duchenne should get access. We believe it can help slow the disease progression for everyone living with this devastating condition. |

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| **12. Are there any potential equality issues that should be taken into account when considering Duchenne muscular dystrophy and givinostat? Please explain if you think any groups of people with this condition are particularly disadvantaged**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here. | |
| **13. Are there any other issues that you would like the committee to consider?** | |

# Part 2: Technical engagement questions for patient experts

## Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

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| **Have comparators been appropriately specified in the submission? (Sections 2.1 and 2.2 of EAR)**<br>This is about the consideration of vamorolone which may displace current corticosteroid use in established clinical management following publication of NICE guidance recommending use of vamorolone in Duchenne muscular dystrophy in January 2025.<br><br>What proportion of people have vamorolone instead of standard corticosteroids? How would this proportion be expected to change over time?<br>What impacts whether people have vamorolone rather than standard corticosteroids? | Yes, established clinical management is an appropriate comparator.<br><br>Vamorolone is a new treatment. It became available to patients through the NHS on April the 16th. Even though it should be available most sites still can't prescribe due to the lack of staffing/pharmacy capacity of the NM service at their hospitals.<br>Vamorolone is not a side effect free steroid. Each patient needs to carefully evaluate the risks and benefits against tradition steroids. |

Patient expert statement

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| How does the clinical effectiveness of vamorolone compare with standard corticosteroids such as prednisone? | As part of the DMD Care UK project we have provided families with the following recommendations to help them evaluate the decision of which option to try.<br>Clinical Recommendations |
| **Definition of 'ambulant' status and implications for generalisability to UK clinical practice (Sections 2.2, 3.3.1.2, 3.3.2.2, 3.4.2.1, 3.4.2.2 of EAR)**<br>How are the following terms defined in people with DMD in NHS practice?<br>• 'ambulant'<br>• 'non-ambulant'<br>• 'late ambulant'<br>• 'early non-ambulant'<br>What clinical measures are used for ambulatory or functional status in DMD in NHS practice?<br>How do these measures differ from what may be used in clinical studies? | We consider people with Duchenne who can weight bare and transfer to be ambulant. They are ambulant until they enter the early non-ambulant stage.<br>Please refer to Project Hercules model for stages and definition of non-ambulant. |
| **Post-hoc selection of givinostat OLE patients (section 3.4.2.1 of EAR)**<br>This is about the patient population used in the open label extension study (OLE). The OLE population included people who had received givinostat in the initial study ("givinostat" group), people who received placebo in EPIDYS ("delayed givinostat") and people who met the criteria for EPIDYS but were not enrolled ("naïve givinostat"). | See charity response |

Patient expert statement

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| How might the efficacy of givinostat differ when excluding people who received placebo in EPIDYS ("delayed givinostat"), compared with including the full OLE population? | |
| **Source of data to inform comparative treatment efficacy (Section 3.4.2.2 of EAR)**<br>This is about how the data used for comparative treatment efficacy in established clinical management may be imbalanced in prognostic factors such as baseline characteristics, type of corticosteroids and inclusion criteria for trials/registry studies compared with the givinostat clinical trial data.<br><br>Which of the following patient populations is likely to be most similar to the patient population in the EPIDYS clinical trial and OLE?<br>• UK registry study<br>• CINRG DHNS registry<br>What are the similarities and differences between these patient populations and the EPIDYS clinical trial and OLE? | The DMD Care UK project was created because the international recommendations published in The Lancet Neurology in 2018, were not deliverable in the NHS. They are widely seen as the North American standard of care.<br><br>DMD Care UK is a UK nationwide initiative to ensure every person living with Duchenne muscular dystrophy (DMD) in the UK has access to the best care, no matter where they live.<br><br>The project took the Lancet recommendations and adapted them to make them deliverable within the NHS.<br><br>As you will read in the Lancet publication there is a different recommended standard of care in North America to the recommendations made in the UK by DMD Care UK.<br><br>CINRGY data is predominantly North Amercain data and includes Becker patients with a milder disease progression.<br><br>It is not appropriate to use historical data as care has evolved over the last 15 years. You can see the differences by comparing the International Lancet recommendations from 2010 and then in 2018.<br><br>UK concurrent North Star data is most appropriate data. |
| **What is the impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints? (Sections 3.4.5, 3.4.3, 9.6 of EAR)** | See charity response |

Patient expert statement

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| **Use of 1.5% discounting (Section 4.2.5 of EAR)** | See charity response |
| **Overestimation of caregiver utility impact (Section 4.2.7 of EAR)**<br>This is about the company's current approach to caregiver health related quality of life.<br>Is caregiver burden expected to increase with disease severity? Would the number of caregivers be expected to increase with disease severity (i.e. between ambulatory and non-ambulatory disease states)? | See charity response<br><br>I do not agree that extending survival of a patient leads to a worsening caregiver HRQOL. See quotes in the charity response from bereaved parents. Life without Jack would be unbearable for our whole family. My whole purpose and world would be gone. It's something I don't even want to begin to imagine. I have found this assumption from the EAG the most difficult to read.<br><br>The longer Jack has been able to remain ambulant and maintain arm function the easier it has been to manage his care. Jack taking Givinostat has improved my quality of life and allowed me to hold down a fulltime job that requires me to frequently travel. Jack can be left at home alone whilst I pop to the shop, go to his brother's game or attend a class. This makes our lives easier.<br><br>The EAG's modelling of the number of people it takes to care for a person with Duchenne is underestimated.<br>From my own experience and that of living within the Duchenne community whilst a patient is ambulant they will generally have 2 parents/caregivers at home, a teaching assistant assigned to them in school full time, after school they will receive budget for |

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| | a personal assistant to provide some care (variation in the number of hours provided due to different local authorities approaches), siblings, grandparents and friends also have to help to share the burden.<br><br>As the disease progresses the number of caregivers increases significantly. People with Duchenne who manage to go to university who are non-ambulant, still have HTMF and no night time NIV have 4 full time carers as part of their care package, they also still have the two parents/caregivers, siblings, grandparents and friends helping them.<br><br>The number of caregivers increases again with the start of night time NIV and then when they move to full time ventilation. See charity response. |
| **Costs and quality of life assumed the same in the full ventilation states and night ventilation states (Sections 4.2.7 and 4.2.8 of EAR)**<br>How would you expect costs and quality of life to compare for people who have full ventilation and people who only have night ventilation? | See charity response |
| **Overestimation by natural history model (NHM) of survival and DMD clinical progression events ( Section 4.2.6 of EAR)**<br>What percentage of people with DMD in England would be expected to survive to:<br>• age 10?<br>• age 20? | This is data we do not have access to. Refer to NS Network. |

Patient expert statement

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| • age 30?<br>• age 40?<br>• age 50?<br>What would be the average age a person with DMD in England would be expected to start ventilation?<br>What would be the average age a person with DMD in England would be expected to start full-time ventilation? | |
| **Mismatch of HERCULES natural history model (NHM) and available randomised controlled trial (RCT) data on givinostat (Section 3.4 and Section 4.2.2 of EAR)**<br>This issue is about how the main outcome of EPIDYS (4SC – i.e. the mean change in the time taken to complete a standard four-stair climb between baseline and 18 months) is not an outcome built into the HERCULES model structure so non-randomised evidence is used to inform treatment effects in the model.<br><br>How often is 4SC used in clinical practice settings to measure functional status?<br><br>How representative is the placebo arm of EPIDYS to NHS clinical practice? | The 4SC has not been used at our local hospital for clinical care management. The NSAA and PUL are used every six months as assessments to help manage care. |
| **Implementation of treatment effect within the economic model (Sections 3.4, 4.2.2 and 4.2.6 of EAR)** | |
| **Are there any important issues that have been missed in EAR?** | |

## Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Givinostat has slowed the disease progression down for me. It's pushing back the devastating milestones of loss that loom heavily ahead. It has helped me keep transferring and keep my HTMF. This is important to me.
- It's allowing me to build an independent future for myself that neither I nor my parents thought I could have when I was diagnosed.
- It has improved my caregiver's quality of life and given my parents the ability to work demanding jobs fulltime.
- The EAG have not understood care giver burden and quality of life and the number of people it takes to care for someone suffering with Duchenne.
- UK real world data is the most appropriate control.

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Tuesday 6 May 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# About you

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| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | Action Duchenne |
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>● the name of the company<br>● the amount<br>● the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>● whether it is ongoing or has ceased. | £15,000 sponsorship funding received from ITF Pharma UK (Italfarmaco Group) towards 2024 Action Duchenne's International Conference.<br>The funding is not ongoing.<br>The purpose of funding is not related to Givinostat for treating symptoms associated with Duchenne muscular dystrophy.<br>With the support from our sponsors and exhibitors, the charity is able to offer free conference tickets to all UK and international Duchenne families. |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry | —---------- <br> Action Duchenne has worked collaboratively with other patient organisations (Duchenne UK and Muscular Dystrophy UK) to produce this submission. <br> **N/A** |

**Table 1 About you**

# Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the EAR.

### Table 2 Key issues

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Have comparators been appropriately specified in the submission? | No | Yes, Established Clinical Management (ECM) is a valid comparator.<br><br>A complication is vamorolone, a corticosteroid which could in theory fall under ECM as it is now recommended by NICE for the treatment of DMD, but which was only very recently made available in the NHS (April 2025). Therefore, there are issues around what evidence and data on vamorolone, if any, could be used in this appraisal. There is limited clinical data available regarding vamorolone and we would be very concerned if this review were to be delayed until sufficient data were to be collected.<br><br>We agree with the EAG's opinion that ataluren is not an appropriate comparator. |
| Definition of 'ambulant' status and implications for generalisability to UK clinical practice | No | The EAG states there is no agreed definition of ambulatory status in DMD, and that categorisation could depend on the assessment or measures used.<br><br>We understand that carefully controlled clinical trials will require certain definitions on |

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| | | ambulation necessary for proper statistical analysis of the clinical data, but we do not consider the measurement of ambulation in clinical trials and in practice settings to meaningfully differ, despite what the EAG reports hearing from clinical advisors. As an example, the four-stair climb is used in clinical trials, but not in practice. The North Star Ambulatory Assessment is used in practice, and is a secondary endpoint in EPIDYS. We consider this a valid approach that incorporates meaningful functional assessments.<br><br>Loss of ambulation is not a discrete binary event, and it can take several weeks before it becomes apparent that an individual has transitioned to a new state. There are many ways to measure this, and we consider the definitions used in the company submission to be valid. Data in the registries and in natural history is collected generally, at best, at 6 month intervals so a discrete date of loss of ambulation is difficult to ascertain.<br><br>In addition, we would note that while we understand that ambulation is a useful milestone in tracking the progression of DMD (thanks in part to the ease of identifying when it is lost), we would add that general muscle function and upper body function are extremely important too. Ultimately all these measures are somewhat arbitrary, but all are capable of measuring loss of muscle and function. They serve as a suitable proxy for disease stage and progression and therefore patient quality of life, which is much more subjective. |
| Post-hoc selection of givinostat OLE patients | No | The EAG suggests an alternative approach would be to include all patients that were included in the open label extension study (OLE) in the unanchored indirect treatment comparison (uITC). In particular, the EAG questions the exclusion of the ‘delayed’ givinostat group – randomly selected patients who had received a placebo during the study, but were moved to givinostat after 18 months. |

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| | | We do not agree with this suggestion by the EAG. Firstly, as this group is already in the analysis as the placebo arm, putting them in again would double count them (likely requiring part of the cohort data to be subject to repeated measures analysis).<br><br>Secondly, by taking part in the clinical trial the 'delayed' givinostat group would be confounded by having had good clinical care in the trial which could impact the outcomes.<br><br>The selection of givinostat OLE patients in the company submission is valid. |
| Source of data to inform comparative treatment efficacy | No | This key issue is linked to key issue 5 – please consider the points we make in key issue 5 here too.<br><br>The EAG suggests using data from the CINRG DHNS registry. We disagree with this suggestion for three reasons: Firstly, the standard of care in the US and the UK differ greatly – the natural history data set is not a like for like comparison. The disparity in standard of care in the US led to the establishment of the DMD Care UK programme that has been accepted by NICE as one of the first two recommendations they will endorse as part of their guideline collaboration project.<br><br>Secondly, the CINRG dataset is now almost 15 years old and does not reflect improvements in outcomes due to better care.<br><br>And thirdly, NICE has specifically asked for relevant UK data and the dataset is now almost 15 years old during which time measures, outcomes and treatments have significantly changed both in the US and elsewhere. |

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| Impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints | No | The EAG notes that the company's main study provides insufficient evidence on longer-term outcomes.<br><br>It is important to remember that DMD's rarity inherently limits available data, and historically, treatment options have been scarce. However, evolving standards of care and emerging therapies are improving outcomes and extending lifespans. Consequently, natural history data is limited, dynamic, and can quickly become outdated. Randomised controlled trial data is sparse and varies internationally. Furthermore, past inconsistencies in standards of care across centers mean that historical data may rely on different measurements. In the UK, outside of trials, patients are often seen only every six months, potentially missing significant within-state progression in routine records (see recommendations in Bushby et al. *Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care.* Lancet Neurol. 2010;9:177–189). Therefore, capturing the detailed longitudinal data the EAG desires, reflecting precise transitions within and between health states in real-world settings for this progressive rare disease, is practically infeasible.<br><br>These constraints mean that the ability to make randomised comparisons on longer-term outcomes is limited. Flexibility is required in using endpoints in natural history data in rare and ultra rare progressive conditions.<br><br>Our recommendation is that the focus is put on care in the UK and endpoints should be mapped to that as best as possible. We consider the company to have done this in an appropriate way in their submission. |

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| Overestimation of caregiver utility impact | No | We disagree with the EAG's approach on this key issue, and believe that caregiver burden and caregiver quality of life (QoL) are being conflated.<br><br>We strongly disagree with the result of the EAG's approach which means that extending the life of patients worsens caregiver QALYs overall. We strongly believe the opposite (that extending the life of patients improves caregiver QALYs overall) is true.<br><br>It's vital to consider health-related quality of life (HRQOL) and the burden of care when evaluating DMD treatments, as these factors are central to a comprehensive QALY assessment. Effective DMD treatment not only benefits the individual but also significantly improves the mental well-being of parents and caregivers, thereby enhancing their HRQOL and their ability to manage the daily demands of caregiving. Furthermore, as individuals with DMD transition to adulthood, the burden and costs of care shift towards social care and services, factors that must be considered. Alleviating the burden of caregiving allows parents to resume their parental role more fully, leading to a further increase in their quality of life.<br><br>HRQOL of parent caregivers is linked to the burden of caregiving but not entirely. Arguably the biggest impact on parent caregiver HRQOL is that of living a life with a severely disabled child, which has a huge impact on daily living, school and education, employment, financial difficulties, anticipatory grief and actual bereavement. This is not confined to one caregiver or even 1.7 caregivers (as the burden of caring might be) but the whole extended family.<br><br>Disappointingly, the EAG did not include the utility decrement for dead patients, otherwise referred to as the bereavement disutility, in the corrected |

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| | | base case. We believe that this is an incorrect decision, and that it does not reflect the lived experiences of parents whose children with DMD have died.<br><br>To demonstrate this we have included three pieces of testimony from bereaved parents:<br>Kaye Hemmings' son Dominic was 25 when he died;<br><br>*"Since I lost my son from DMD over 5 years ago I don't live, I exist.*<br><br>*"I find it hard to get out of bed each day. It's another day to get through. The most mundane of tasks feel like climbing a mountain.*<br><br>*"I can't remember a time that I have been truly happy since he left us.*<br><br>*"The hole he left is too big to fill.*<br><br>*"I have had a few cancer scares since he passed away and when the nurses told me I was ok they didn't understand why I wasn't happy. I thought it was a way out for me to be with him again.*<br><br>*"If I didn't have other children I wouldn't be here.*<br><br>*"When he left me our car was taken away weeks later, as was all of his equipment and I was thrown into living a 'normal' life and expected to carry on like nothing happened.*<br><br>*"Grieving doesn't have an expiry date. And anyone who feels that my life quality would improve has never had to go through losing a child and had never met my son who deserved so much more from life than he got."*<br><br>Michelle Beckett's son Ryan was 29 when he died. |

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| | | *“Losing my child has changed everything about my life.*<br><br>*“As a full-time caregiver for 29 years, I have dedicated my life to ensure my son gets the best care he deserves. I’ve fought battles no mother should have to fight.*<br><br>*“I wake up everyday & my son is no longer here. I go to sleep & I go over the traumatic way he died. I have visions of my son laid in his coffin, wearing his favoured football shirt. No mother should have to witness that!*<br><br>“*I have no idea how I survive another day without him, but I do just that, survive.*<br><br>*“My heart is broken, forever. I have never felt a pain like it.*<br>*“As a full-time caregiver for 29 years, I have dedicated my life to ensure my son gets the best care he deserves. I’ve fought battles no mother should have to fight.*<br><br>*“I wake up everyday & my son is no longer here. I go to sleep & I go over the traumatic way he died. I have visions of my son laid in his coffin, wearing his favoured football shirt. No mother should have to witness that!*<br><br>*“I have no idea how I survive another day without him, but I do just that, survive.*<br><br>*“My heart is broken, forever. I have never felt a pain like it.*<br><br>*“It’s overwhelming, it’s emotional, & the effect it has had on my body is incredible.* |

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| | | *“Grief tries to drag me down everyday, but I try to fight back, everyday, it’s exhausting.”*<br><br>Janet Bloor’s son Philip was 28 when he died.<br><br>*“Once a boy/adult dies a caregiver’s life is one of devastation and loss you never get over – what you would give to be getting up in the middle of the night – your turn to help him go to the toilet.*<br><br>*“Your world, your meaning in life has gone, you are a shell of yourself. Quality of life improves: what a disgusting way to describe your unbearable grief.”* |

## Additional issues

**All:** Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

**Table 3 Additional issues from the EAR**

| Issue from the EAR | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|

## Summary of changes to the company's cost-effectiveness estimate(s)

**Company only:** If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

**Table 4 Changes to the company's cost-effectiveness estimate**

| Key issue(s) in the EAR that the change relates to | Company's base case before technical engagement | Change(s) made in response to technical engagement | Impact on the company's base-case incremental cost-effectiveness ratio (ICER) |
|---|---|---|---|

**Sensitivity analyses around revised base case**

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Tuesday 6 May 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# About you

### Table 1 About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | Duchenne UK |
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | [redacted] |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry | **N/A** |

## Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the EAR.

**Table 2 Key issues**

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Have comparators been appropriately specified in the submission? (1) | No | Yes, Established Clinical Management (ECM) is a valid comparator.<br><br>A complication is vamorolone, a corticosteroid which could in theory fall under ECM as it is now recommended by NICE for the treatment of DMD, but which was only very recently made available in the NHS. Therefore there are issues around what evidence and data on vamorolone, if any, could be used in this appraisal. There is limited clinical data available regarding vamorolone and we would be very concerned if this review were to be delayed until sufficient data were to be collected<br><br>We agree with the EAG's opinion that ataluren is not an appropriate comparator. |
| Definition of 'ambulant' status and implications for generalisability to UK clinical practice (2) | No | The EAG states there is no agreed definition of ambulatory status in DMD, and that categorisation could depend on the assessment or measure used.<br><br>We understand that carefully controlled clinical trials will require certain definitions on ambulation, but we do not consider the measurement of ambulation in clinical |

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| | | trials and in practice settings to meaningfully differ, despite what the EAG reports hearing from clinical advisors. As an example, the four-stair climb is used in clinical trials, but not in practice. The North Star Ambulatory Assessment is used in practice, and is a secondary endpoint in EPIDYS. We consider this a valid approach.<br><br>Loss of ambulation is not a discrete binary event, and it can take several weeks before it becomes apparent that an individual has transitioned to a new state. There are many ways to measure this, and we consider the definitions used in the company submission to be valid. Data in the registries and in natural history is collected generally at best at 6 month intervals so a discrete date of loss of ambulation is difficult to ascertain.<br><br>In addition, we would note that while we understand that ambulation is a useful milestone in tracking the progression of DMD (thanks in part to the ease of identifying when it is lost), we would add that general muscle function and upper body function are extremely important too. Ultimately all these measures are capable of measuring loss of muscle and function. They serve as a suitable proxy for disease stage and progression and also therefore patient quality of life. |
| Post-hoc selection of givinostat OLE patients (3) | No | The EAG suggests an alternative approach would be to include all patients that were included in the open label extension study (OLE) in the unanchored indirect treatment comparison (uITC). In particular, the EAG questions the exclusion of the 'delayed' givinostat group – randomly selected patients who had received a placebo during the study, but were moved to givinostat after 18 months.<br><br>We do not agree with this suggestion by the EAG. Firstly, this group is already in the analysis as the placebo arm, so would be double counted. Secondly, by taking part in the clinical trial the 'delayed' givinostat group outcomes might be confounded by having had good clinical care in the trial.. |

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| | | The selection of givinostat OLE patients in the company submission is valid. |
| Source of data to inform comparative treatment efficacy (4) | No | This key issue is linked to key issue 5 – please consider the points we make in key issue 5 here too.<br><br>The EAG suggests using data from the CINRG DHNS registry as it has one similar outcome measure. We disagree with this suggestion for three reasons: firstly the standard of care in the US and the UK differ widely – the natural history data set is not a like for like comparison. The disparity in standard of care in the US is why Duchenne UK set up the DMD Care UK programme that has been accepted by NICE as one of the first two recommendations they will endorse as part of their guideline collaboration project.<br><br>Secondly the CINRG dataset is now almost 15 years old and may not reflect improvements in outcomes due to better care.<br><br>And thirdly, NICE has specifically asked for relevant UK data. The data is from the US and the age of the dataset whilst helpful for numbers, will mean measures, outcomes and treatments in that dataset will have significantly changed both in the US and elsewhere. |
| Impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints (5) | No | The EAG notes that the company's main study provides insufficient evidence on longer-term outcomes.<br><br>Remember that DMD is a rare disease, which limits the data available and has had historically very limited treatment options. Progression and outcomes are evolving thanks to improvements in standards of care and new treatments on the horizon – only recently have patients started living longer. Natural history data is limited, evolving, and can become out of date quickly. Sources for randomised comparison |

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| | | are sparse, and vary between countries. Previous differing standards between centres also mean different measures may have been made. Outside of clinical trials, patients in the UK will rarely be seen more frequently than once every 6 months and as they get older even less frequently (see recommendations in Bushby et al. *Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care.* Lancet Neurol. 2010;9:177–189) during which time significant progression can occur within a health state and may not be captured in clinical/natural history records. Clinicians do not routinely collect everything and patients can refuse to be measured. This means that in real world settings as in most progressive rare diseases it is not actually possible to capture highly detailed longitudinal data (which the EAG believe and we agree would be helpful) that captures when patients change within a health state or when they move from one state to the next.<br><br>These constraints mean that the ability to make randomised comparisons on longer-term outcomes is limited. Flexibility is required in using and interpreting endpoints in natural history data in rare and ultra rare progressive conditions.<br><br>Our recommendation is that the focus is put on care in the UK and endpoints should be mapped to that as best as possible. We consider the company to have done this in the most appropriate way in their submission. |
| Use of 1.5% discounting (6) | No | We note that NICE's recommendation for the following HTAs applied a 1.5% discount rate. DMD, like the conditions below, is a rare and life-limiting condition, and they should be treated similarly.<br><br>Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency (HST1)<br>Eculizumab for treating atypical haemolytic uraemic syndrome (HST7)<br>Onasemnogene abeparvovec for treating spinal muscular atrophy (HST15) |

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| | | Dinutuximab beta for treating neuroblastoma (TA538) |
| Overestimation of caregiver utility impact (7) | No | We disagree with the EAG's approach on this key issue, and believe that caregiver burden and caregiver quality of life (QoL) are being conflated.<br><br>We strongly disagree with the result of the EAG's approach which means that extending the life of patients worsens caregiver QALYs overall. We believe the opposite (that extending the life of patients improves caregiver QALYs overall) is true.<br><br>Whilst we recognise evidence on caregiver health related quality of life, is sparse, we know from parent feedback that the burden of caregiving and its impact on health related quality of life (HRQOL) increases with progression of disease so it makes sense that preventing and slowing progression to later stages would give a benefit in terms of HRQOL of carers.<br><br>What's important is HRQOL, as well as burden which should be part of the QALY calculation. Treating DMD properly means parents and caregivers can enjoy a better mental state than they otherwise would, increasing HRQOL and are better able to cope. As young men transition to adulthood, the burden and costs of care move into social care and social services (which are not taken account of in HTA). The relief of care giving burden enables parent caregivers to become parents again and thus quality of life increases.<br><br>HRQOL of parent caregivers is linked to burden of caregiving but not entirely. Arguably the biggest impact on parent caregiver HRQOL is that of living a life with a severely disabled child, which has a huge impact on daily living, school and education, employment, financial difficulties, anticipatory grief and actual bereavement. This is not confined to one caregiver or even 1.7 caregivers (as burden of caring might be) but the whole extended family. |

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| | | Both parents will be affected by the diagnosis, and both are often involved in caregiving as are other family members. The mental health of each parent, and the extended family who may be involved in caregiving, will be impacted. It is unfair to assume that only a single parent's mental health would be affected until a patient reaches a certain progression.<br><br>Disappointingly, the EAG did not include the utility decrement for patients who have died otherwise referred to as the bereavement disutility, in the corrected base case. We believe that this is an incorrect decision, and that it does not reflect the lived experiences of parents whose children with DMD have died. This problem is known as the caregiver QALY trap, and is well explored in literature[1], including specifically in relation to Duchenne muscular dystrophy[2]. No published work is available on bereavement impact on HRQOL for parents. ISPOR 2024 had a presentation on bereavement in SMA, but this has not been published[3].<br><br>To further demonstrate this we have gathered testimony from bereaved parents.<br><br>Kaye Hemmings' son Dominic was 25 when he died;<br><br>*"Since I lost my son from DMD over 5 years ago I don't live, I exist.*<br><br>*"I find it hard to get out of bed each day. It's another day to get through. The most mundane of tasks feel like climbing a mountain.* |

[1] https://link.springer.com/article/10.1007/s40273-023-01316-0
[2] https://www.ispor.org/docs/default-source/euro2024/iqviaispor-caregiver-qaly-trap-dmd-v2-02024sandhufinal145788-pdf.pdf
[3] https://www.ispor.org/docs/default-source/euro2024/should-hta-include-the-bereavement-effect-on-hrqol.pdf

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| | | *“I can't remember a time that I have been truly happy since he left us.*<br><br>*“The hole he left is too big to fill.*<br><br>*“I have had a few cancer scares since he passed away and when the nurses told me I was ok they didn't understand why I wasn't happy. I thought it was a way out for me to be with him again.*<br><br>*“If I didn't have other children I wouldn't be here.*<br><br>*“When he left me our car was taken away weeks later, as was all of his equipment and I was thrown into living a 'normal' life and expected to carry on like nothing happened.*<br><br>*“Grieving doesn't have an expiry date. And anyone who feels that my life quality would improve has never had to go through losing a child and had never met my son who deserved so much more from life than he got.”*<br><br>Michelle Beckett’s son Ryan was 29 when he died.<br><br>*“Losing my child has changed everything about my life.*<br><br>*“As a full-time caregiver for 29 years, I have dedicated my life to ensure my son gets the best care he deserves. I’ve fought battles no mother should have to fight.* |

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| | | *“I wake up everyday & my son is no longer here. I go to sleep & I go over the traumatic way he died. I have visions of my son laid in his coffin, wearing his favoured football shirt. No mother should have to witness that!*<br><br>*“I have no idea how I survive another day without him, but I do just that, survive.*<br><br>*“My heart is broken, forever. I have never felt a pain like it.*<br><br>*“It’s overwhelming, it’s emotional, & the effect it has had on my body is incredible.*<br><br>*“Grief tries to drag me down everyday, but I try to fight back, everyday, it’s exhausting.”*<br><br>Janet Bloor’s son Philip was 28 when he died.<br><br>*“Once a boy/adult dies a caregiver’s life is one of devastation and loss you never get over – what you would give to be getting up in the middle of the night – your turn to help him go to the toilet.*<br><br>*“Your world your meaning in life has gone you are a shell of yourself. Quality of life improves: what a disgusting way to describe your unbearable grief.”*<br><br>Phillippa Farrant son’s Dan was 27 when he died.<br><br>*“As a bereaved mum, who lost her son in 2019, I am appalled to hear the suggestion that a child's life-saving treatment should be denied because their death might ease a caregiver's burden. How presumptuous of someone who* |

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| | | *hasn't lost their child to comment in this way! This surely undermines the most basic principles of medical ethics and human rights. We should not in any circumstance weigh the value of someone's life against another person's convenience or well-being—that's a dangerous and dehumanizing precedent. I can safely assure you that in no way has my quality of life gone up - day to day life might be easier from the point of view that Dan is not having to be looked after, but the loss never goes away, and he is certainly missed by all who knew him. If there are treatments, then the people that should find a way to get these drugs to the affected people in a timely and empathetic way without disregard to all those who care for them."* |

## Additional issues

**All:** Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

**Table 3 Additional issues from the EAR**

| Issue from the EAR | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|
| Costs and quality of life assumed the same in the full ventilation states and night ventilation states | Key issue 8 | No | ITF have taken conservative approach by treating states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") to be the same.<br><br>It is highly likely that state 8 is more impactful in cost and utility impacts than state 7, but we also recognise that data on this is sparse.<br><br>To illustrate the differences between the ventilations state, Dr Jon Hastie – an adult living with DMD – has provided the following testimony.<br><br>*I have experienced both the full ventilation state and night ventilation state, as an individual living with Duchenne muscular dystrophy and having progressed through the stages. In the night ventilation stage, no one apart from my family and carers knew that I used ventilation. Now in the full ventilation stage, I have a mask over my face at all times. I simply cannot overstate how inaccurate the claim is that these two states are the same.* |

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| | | | *There are significant differences in both cost and quality of life between these two states. Quite simply for cost, eligibility criteria for NHS continuing healthcare is to score severely in two domains. People with DMD at this stage will usually score severely in the mobility domain by default. On the breathing domain the score is more variable, and it is only in the full ventilation state that eligibility is guaranteed. This makes the cost of providing care a cost to the NHS, significantly greater than social care.*<br><br>*In the full ventilation state, any time off the ventilator endangers life. On night ventilation, during the day I didn't require round-the-clock care, and could be left on my own for several hours during the day. Overnight, I didn't require waking night care, and a carer sleeping nearby was sufficient in the event of any difficulties. This meant significantly lower costs for care staff and varied as my condition progressed - from approximately £40k-£100k per year.*<br><br>*Currently I am in the full ventilation state and require round-the-clock care from two personal assistants. This includes waking nights. It is critical that there is always a carer with me as a ventilator malfunction or disconnection could otherwise mean death. The overall cost of my care package is around £250-300k per year.*<br><br>*In terms of quality-of-life, my anxiety has increased dramatically moving in to the full ventilation state. I live with the constant fear that if the ventilator malfunctions my carer cannot fix the issue or does not realise. I know that people with my condition have died where this has happened and they have not had adequate support. I am no longer able to enjoy any privacy as any time alone is life-threatening. As I manage my own social care support and don't have family nearby, I have to spend hours every day managing my care package to ensure there is cover in emergencies. This interrupts every enjoyable part of my life - for example at a family birthday recently I had to step away from the celebrations in order to fix my care package so that I wouldn't be on my own within the next few hours. The ability to have intimacy is significantly impaired as the ventilator gets in the way of intimate activities as the mask is a permanent feature on my face. Every time I leave the house I* |

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| | | | *am stared at by passers-by, who think I am either infectious or belong in a hospital ward. With a mask on my face at all times it is difficult to shower, get a haircut, clean my teeth, eat, be dressed and undressed or use a hydrotherapy pool. It has significantly impacted on my speech and ability to swallow while eating with a ventilator.*<br>*I would give absolutely anything to move back to the night ventilation state or have preserved it for a little longer.* |
| Overestimation by NHM of survival and DMD clinical progression events (9) | Key issue 9 | No | This is a rare condition with limited data available and some conflicting results from RWE, and the clinicians' view is probably most representative of survival. Timing of clinical progression events will also vary, depending on how it is captured. Again – a degree of pragmatism and common sense when reviewing the evidence is required in any rare paediatric progressive condition. |
| Mismatch of HERCULES NHM and available RCT data on givinostat | Key issue 10 | | HERCULES NHM is based on as much evidence that was possible to access at the time. Any NH data will be unlikely to directly match results in an RCT, as the element of clinical trial participation can improve outcomes by increased levels of care and measurement. |
| Implementation of treatment effect within the economic model | Key issue 11 | No | We are concerned that the EAG has misunderstood the HERCULES model. The differences in this review versus the previous review by a different EAG for vamolorone are concerning and illustrate a lack of understanding and consistency in EAG capability. The HERCULES model was built to provide a comprehensive gold standard economic model (with NICE input) and to therefore avoid multiple reviews which is not a cost-effective use of EAG or NICE resources. |
| HST v STA | | No | This HTA has been routed down the STA pathway. While it is being considered by the HST committee, it is still bound to the rules and assessment criteria also used for general, population-wide conditions such as diabetes and |

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| | | | high blood pressure. Despite the indication being for a rare and severe paediatric life-limiting disease.<br><br>We are very disappointed that this has not been routed down the much more suitable and flexible HST pathway, and note that due to the most recent changes to HST eligibility DMD – a condition affecting only 2,500 people in the UK – is too common to be considered rare. This is a devastating, rare and very severe fatal disease in children with huge impact on individuals, families, clinicians and society so we are at a loss to understand why it should not be treated as such. |
| Definition of ambulation | | No | Duchenne UK preference when measuring ambulation would be whether the individual can stand aided. This would correctly capture patients who are in the transfer stage, which should count as ambulant in this context as the individual retains vital and demonstrable muscle function in their lower body which should be preserved. For example, being able to stand aided, e.g. with a frame or railing, can mean that an individual can go to the toilet alone (a notable part of maintaining independence for many). |

## Summary of changes to the company's cost-effectiveness estimate(s)

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**Table 4 Changes to the company's cost-effectiveness estimate**

| Key issue(s) in the EAR that the change relates to | Company's base case before technical engagement | Change(s) made in response to technical engagement | Impact on the company's base-case incremental cost-effectiveness ratio (ICER) |
|---|---|---|---|
| Insert key issue number and title as described in the EAR | Briefly describe the company's original preferred assumption or analysis | Briefly describe the change(s) made in response to the EAR | Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER. |
| Insert key issue number and title as described in the EAR | … | … | [INSERT / DELETE ROWS AS REQUIRED] |
| Company's base case following technical engagement (or revised base case) | Incremental QALYs: [QQQ] | Incremental costs: [£££] | Please provide company revised base-case ICER |

**Sensitivity analyses around revised base case**

PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

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Do not include medical information about yourself or another person that could identify you or the other person.

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Thank you for your time.

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**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# About you

## Table 1 About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | Muscular Dystrophy UK<br><br>This response has been developed in partnership with Duchenne UK and Action Duchenne. |
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | **ITF Pharma Ltd**<br>- £ 4,125+ VAT for Bronze sponsorship – 18th UK Neuromuscular Translational Research Conference 2025, March 2025<br><br>**PTC Therapeutics**<br>- £16K + VAT as series sponsor for MDUK's Virtual Seminar Series, August 2024 |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry | None |

## Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the EAR.

### Table 2 Key issues

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Have comparators been appropriately specified in the submission? (1) | No | Yes, Established Clinical Management (ECM) is a valid comparator.<br><br>A complication is vamorolone, a corticosteroid which could in theory fall under ECM as it is now recommended by NICE for the treatment of DMD, but which was only very recently made available in the NHS. Therefore there are issues around what evidence and data on vamorolone, if any, could be used in this appraisal. There is limited clinical data available regarding vamorolone and we would be very concerned if this review were to be delayed until sufficient data were to be collected.<br><br>We agree with the EAG's opinion that ataluren is not an appropriate comparator. |
| Definition of 'ambulant' status and implications for generalisability to UK clinical practice (2) | No | The EAG states there is no agreed definition of ambulatory status in DMD, and that categorisation could depend on the assessment or measure used.<br><br>We understand that carefully controlled clinical trials will require certain definitions on ambulation, but we do not consider the measurement of ambulation in clinical |

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| | | trials and in practice settings to meaningfully differ, despite what the EAG reports hearing from clinical advisors. As an example, the four-stair climb is used in clinical trials, but not in practice. The North Star Ambulatory Assessment is used in practice, and is a secondary endpoint in EPIDYS. We consider this a valid approach.<br><br>Loss of ambulation is not a discrete binary event, and it can take several weeks before it becomes apparent that an individual has transitioned to a new state. There are many ways to measure this, and we consider the definitions used in the company submission to be valid. Data in the registries and in natural history is collected generally at best at 6 month intervals so a discrete date of loss of ambulation is difficult to ascertain.<br><br>In addition, we would note that while we understand that ambulation is a useful milestone in tracking the progression of DMD (thanks in part to the ease of identifying when it is lost), we would add that general muscle function and upper body function are extremely important too. Ultimately all these measures are somewhat arbitrary, but all are capable of measuring loss of muscle and function. They serve as a suitable proxy for disease stage and progression and also therefore patient quality of life, which is much more subjective. |
| Post-hoc selection of givinostat OLE patients (3) | No | The EAG suggests an alternative approach would be to include all patients that were included in the open label extension study (OLE) in the unanchored indirect treatment comparison (uITC). In particular, the EAG questions the exclusion of the 'delayed' givinostat group – randomly selected patients who had received a placebo during the study, but were moved to givinostat after 18 months.<br><br>We do not agree with this suggestion by the EAG. Firstly, as this group is already in the analysis as the placebo arm, putting them in again would double count them. Secondly, by taking part in the clinical trial the 'delayed' givinostat group would be |

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| | | confounded by having had good clinical care in the trial which could impact the outcomes.<br><br>The selection of givinostat OLE patients in the company submission is valid. |
| Source of data to inform comparative treatment efficacy (4) | No | This key issue is linked to key issue 5 – please consider the points we make in key issue 5 here too.<br><br>The EAG suggests using data from the CINRG DHNS registry. We disagree with this suggestion for three reasons: firstly the standard of care in the US and the UK differ widely – the natural history data set is not a like for like comparison. The disparity in standard of care in the US is why Duchenne UK set up the DMD Care UK programme that has been accepted by NICE as one of the first two recommendations they will endorse as part of their guideline collaboration project.<br><br>Secondly the CINRG dataset is now almost 15 years old and does not reflect improvements in outcomes due to better care.<br><br>And thirdly, NICE has specifically asked for relevant UK data and the dataset is now almost 15 years old during which time measures, outcomes and treatments have significantly changed both in the US and elsewhere. |
| Impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints (5) | No | The EAG notes that the company's main study provides insufficient evidence on longer-term outcomes.<br><br>Remember that DMD is a rare disease, which limits the data available and has had historically very limited treatment options. Progression and outcomes are evolving thanks to improvements in standards of care and new treatments on the horizon – only recently have patients started living longer. Natural history data is limited, evolving, and can become out of date quickly. Sources for randomised comparison |

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| | | are sparse, and vary between countries. Previous differing standards between centres also mean different measures may have been made. Outside of clinical trials, patients in the UK will rarely be seen more frequently than once every 6 months (see recommendations in Bushby et al. *Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care.* Lancet Neurol. 2010;9:177–189) during which time significant progression can occur within a health state and may not be captured in clinical/natural history records. This means that in real world settings as in most progressive rare diseases it is not actually possible to capture highly detailed longitudinal data (which the EAG believe would be helpful) that captures when patients change within a health state or when they move from one state to the next.<br><br>These constraints mean that the ability to make randomised comparisons on longer-term outcomes is limited. Flexibility is required in using endpoints in natural history data in rare and ultra rare progressive conditions.<br><br>Our recommendation is that the focus is put on care in the UK and endpoints should be mapped to that as best as possible. We consider the company to have done this in the most appropriate way in their submission. |
| Use of 1.5% discounting (6) | | / |
| Overestimation of caregiver utility impact (7) | No | We disagree with the EAG's approach on this key issue, and believe that caregiver burden and caregiver quality of life (QoL) are being conflated.<br><br>We strongly disagree with the result of the EAG's approach which means that extending the life of patients worsens caregiver QALYs overall. We believe the opposite (that extending the life of patients improves caregiver QALYs overall) is true. |

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| | | What's important is health related quality of life (HRQOL), as well as burden which should be part of the QALY calculation. Treating DMD properly means parents and caregivers can enjoy a better mental state than they otherwise would, increasing HRQOL and are better able to cope. As young men transition to adulthood, the burden and costs of care move into social care and social services which are not taken account of. The relief of care giving burden enables parent caregivers to become parents again and thus quality of life increases.<br><br>HRQOL of parent caregivers is linked to burden of caregiving but not entirely. Arguably the biggest impact on parent caregiver HRQOL is that of living a life with a severely disabled child, which has a huge impact on daily living, school and education, employment, financial difficulties, anticipatory grief and actual bereavement. This is not confined to one caregiver or even 1.7 caregivers (as burden of caring might be) but the whole extended family.<br><br>Both parents will be affected by the diagnosis, and both are often involved in caregiving. The mental health of each parent, and the extended family who may be involved in caregiving from time to time, will be impacted. It is unfair to assume that only a single parent's mental health would be affected until a patient reaches a certain progression.<br><br>Disappointingly, the EAG did not include the utility decrement for dead patients, otherwise referred to as the bereavement disutility, in the corrected base case. We believe that this is an incorrect decision, and that it does not reflect the lived experiences of parents whose children with DMD have died. This problem is known as the caregiver QALY trap, and is well explored in literature[1], including specifically in relation to Duchenne muscular dystrophy[2]. |

[1] https://link.springer.com/article/10.1007/s40273-023-01316-0
[2] https://www.ispor.org/docs/default-source/euro2024/iqviaispor-caregiver-qaly-trap-dmd-v2-02024sandhufinal145788-pdf.pdf

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| | | To further demonstrate this we have gathered testimony from bereaved parents.<br><br>Kaye Hemmings' son Dominic was 25 when he died;<br><br>*"Since I lost my son from DMD over 5 years ago I don't live, I exist.*<br><br>*"I find it hard to get out of bed each day. It's another day to get through. The most mundane of tasks feel like climbing a mountain.*<br><br>*"I can't remember a time that I have been truly happy since he left us.*<br><br>*"The hole he left is too big to fill.*<br><br>*"I have had a few cancer scares since he passed away and when the nurses told me I was ok they didn't understand why I wasn't happy. I thought it was a way out for me to be with him again.*<br><br>*"If I didn't have other children I wouldn't be here.*<br><br>*"When he left me our car was taken away weeks later, as was all of his equipment and I was thrown into living a 'normal' life and expected to carry on like nothing happened.* |

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| | | *“Grieving doesn't have an expiry date. And anyone who feels that my life quality would improve has never had to go through losing a child and had never met my son who deserved so much more from life than he got.”*<br><br>Michelle Beckett’s son Ryan was 29 when he died.<br><br>*“Losing my child has changed everything about my life.*<br><br>*“As a full-time caregiver for 29 years, I have dedicated my life to ensure my son gets the best care he deserves. I’ve fought battles no mother should have to fight.*<br><br>*“I wake up everyday & my son is no longer here. I go to sleep & I go over the traumatic way he died. I have visions of my son laid in his coffin, wearing his favoured football shirt. No mother should have to witness that!*<br><br>*“I have no idea how I survive another day without him, but I do just that, survive.*<br><br>*“My heart is broken, forever. I have never felt a pain like it.*<br><br>*“It’s overwhelming, it’s emotional, & the effect it has had on my body is incredible.*<br><br>*“Grief tries to drag me down everyday, but I try to fight back, everyday, it’s exhausting.”*<br><br>Janet Bloor’s son Philip was 28 when he died. |

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| | | *“Once a boy/adult dies a caregiver’s life is one of devastation and loss you never get over – what you would give to be getting up in the middle of the night – your turn to help him go to the toilet.*<br><br>*“Your world your meaning in life has gone you are a shell of yourself. Quality of life improves: what a disgusting way to describe your unbearable grief.”*<br><br>Phillippa Farrant son’s Dan was 27 when he died.<br><br>*“As a bereaved mum, who lost her son in 2019, I am appalled to hear the suggestion that a child's life-saving treatment should be denied because their death might ease a caregiver's burden. How presumptuous of someone who hasn’t lost their child to comment in this way! This surely undermines the most basic principles of medical ethics and human rights. We should not in any circumstance weigh the value of someone’s life against another person’s convenience or well-being—that’s a dangerous and dehumanizing precedent. I can safely assure you that in no way has my quality of life gone up - day to day life might be easier from the point of view that Dan is not having to be looked after, but the loss never goes away, and he is certainly missed by all who knew him. If there are treatments, then the people that should find a way to get these drugs to the affected people in a timely and empathetic way without disregard to all those who care for them.”* |

## Additional issues

**All:** Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

**Table 3 Additional issues from the EAR**

| Issue from the EAR | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|
| Costs and quality of life assumed the same in the full ventilation states and night ventilation states | Key issue 8 | No | ITF have taken conservative approach by treating states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") to be the same.<br><br>It is highly likely that state 8 is more impactful in cost and utility impacts than state 7, but we also recognise that data on this is sparse.<br><br>To illustrate the differences between the ventilations state, Dr Jon Hastie – an adult living with DMD – has provided the following testimony.<br><br>*"I have experienced both the full ventilation state and night ventilation state, as an individual living with Duchenne muscular dystrophy and having progressed through the stages. In the night* |

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| | | | *ventilation stage, no one apart from my family and carers knew that I used ventilation. Now in the full ventilation stage, I have a mask over my face at all times. I simply cannot overstate how inaccurate the claim is that these two states are the same.*<br><br>*There are significant differences in both cost and quality of life between these two states. Quite simply for cost, eligibility criteria for NHS continuing healthcare is to score severely in two domains. People with DMD at this stage will usually score severely in the mobility domain by default. On the breathing domain the score is more variable, and it is only in the full ventilation state that eligibility is guaranteed. This makes the cost of providing care a cost to the NHS, significantly greater than social care.*<br><br>*In the full ventilation state, any time off the ventilator endangers life. On night ventilation, during the day I didn't require round-the-clock care, and could be left on my own for several hours during the day. Overnight, I didn't require waking night care, and a carer sleeping nearby was sufficient in the event of any difficulties. This meant significantly lower costs for care staff and varied as my condition progressed - from approximately £40k-£100k per year.*<br><br>*Currently I am in the full ventilation state and require round-the-clock care from two personal assistants. This includes waking nights. It is critical that there is always a carer with me as a ventilator malfunction or disconnection could otherwise mean death. The overall cost of my care package is around £250-300k per year.*<br><br>*In terms of quality-of-life, my anxiety has increased dramatically moving in to the full ventilation state. I live with the constant fear that if the ventilator malfunctions my carer cannot fix the issue or does not realise. I know that people with my condition have died where this has happened and they have not had adequate support. I am no longer able to enjoy any privacy as any time* |

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| | | | *alone is life-threatening. As I manage my own social care support and don't have family nearby, I have to spend hours every day managing my care package to ensure there is cover in emergencies. This interrupts every enjoyable part of my life - for example at a family birthday recently I had to step away from the celebrations in order to fix my care package so that I wouldn't be on my own within the next few hours. The ability to have intimacy is significantly impaired as the ventilator gets in the way of intimate activities as the mask is a permanent feature on my face. Every time I leave the house I am stared at by passers-by, who think I am either infectious or belong in a hospital ward. With a mask on my face at all times it is difficult to shower, get a haircut, clean my teeth, eat, be dressed and undressed or use a hydrotherapy pool. It has significantly impacted on my speech and ability to swallow while eating with a ventilator.*<br>*I would give absolutely anything to move back to the night ventilation state or have preserved it for a little longer."* |
| Overestimation by NHM of survival and DMD clinical progression events (9) | Key issue 9 | No | This is a rare condition with limited data available and some conflicting results from RWE, and the clinicians' view is probably most representative of survival. Timing of clinical progression events will also vary, depending on how it is captured. Again – a degree of pragmatism and common sense when reviewing the evidence is required in any rare paediatric progressive condition. |
| Mismatch of HERCULES NHM and available RCT data on givinostat | Key issue 10 | | HERCULES NHM is based on as much evidence that was possible to access at the time. Any NH data will be unlikely to directly match results in an RCT, as the element of clinical trial participation can improve outcomes by increased levels of care and measurement. |

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| Implementation of treatment effect within the economic model | Key issue 11 | No | We are concerned that the EAG has misunderstood the HERCULES model. The differences in the review versus the previous review by a different EAG for vamolorone are concerning and illustrates a lack of understanding. The HERCULES model was built to provide a comprehensive gold standard economic model (with NICE input) and to therefore avoid multiple reviews which is not a cost-effective use of EAG or NICE resources. |

## Summary of changes to the company's cost-effectiveness estimate(s)

**Company only:** If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

**Table 4 Changes to the company's cost-effectiveness estimate**

| Key issue(s) in the EAR that the change relates to | Company's base case before technical engagement | Change(s) made in response to technical engagement | Impact on the company's base-case incremental cost-effectiveness ratio (ICER) |
|---|---|---|---|
| Insert key issue number and title as described in the EAR | Briefly describe the company's original preferred assumption or analysis | Briefly describe the change(s) made in response to the EAR | Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER. |
| Insert key issue number and title as described in the EAR | … | … | [INSERT / DELETE ROWS AS REQUIRED] |
| Company's base case following technical engagement (or revised base case) | Incremental QALYs: [QQQ] | Incremental costs: [£££] | Please provide company revised base-case ICER |

**Sensitivity analyses around revised base case**
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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# About you

### Table 1 About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | Association of British Neurologists |
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | **I have not received any funding from the company brining the treatment to NICE.**<br>**I have not received any funding from any comparator treatment company.** |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry | **N/A** |

## Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the EAR.

### Table 2 Key issues

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Have comparators been appropriately specified in the submission? | No | I think the authors of the EAR are right to raise the issue of the likely increasing use of vamorolone, especially for those earlier in their disease course. I am however conscious that there are always “moving targets” in terms of what constitutes ECM. Whilst updating the analysis to take in to account the impacts of the use of vamorolone as part of ECM should be considered, I would be concerned about the additional delays that this endeavour might bring to this process and the consequent impact on patients. |
| Definition of ‘ambulant’ status and implications for generalisability to UK clinical practice | No | I only see patients after ambulation has (clearly) been lost and I am therefore not an expert on the issue. I agree that there would be benefits to establishing a standardised definition of these terms. It is not particularly unusual for definitions used in clinical trials to permeate in to clinical practice. |
| Post-hoc selection of givinostat OLE patients | No | The comments in the EAR on this subject appear reasonable. The complex statistical discussion is beyond my level of expertise, but a reasonable case is made by the authors of the EAR that bias may be introduced by post-hoc selection of certain groups. |
| Source of data to inform comparative treatment efficacy | No | I feel unable to comment on this. |

| | | |
|---|---|---|
| Impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints | **No** | I feel unable to comment on this. |
| Use of 1.5% discounting | No | I am not an expert on this particular issue, but do agree with the comment: “The EAG notes that there is no evidence of this long-term benefit from either RCT or cohort studies”. |
| Overestimation of caregiver utility impact | No | I am not an expert in this quite complex statistical issue, but the authors of the EAR do appear to make a reasonable argument for potential over-estimation of caregiver utility impact. |

## Additional issues

**All:** Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

**Table 3 Additional issues from the EAR**

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|---|---|---|---|
| Additional issue 1: Insert additional issue | Please indicate the section(s) of the EAR that discuss this issue | Yes/No | Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making |
| Additional issue 2: Insert additional issue | Please indicate the section(s) of the EAR that discuss this issue | Yes/No | Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making |
| Additional issue N: Insert additional issue | | | [INSERT / DELETE ROWS AS REQUIRED] |

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**Sensitivity analyses around revised base case**

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**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# About you

### Table 1 About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle, UK |
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | Speaker honoraria from Dyne – 2840 £, October 2024<br>Member of the DSMB for Antisense Therapeutics – funding to Newcastle University - completed<br>Member of advisory boards for NS Pharma, Santhera, Dyne, Edgewise – funding to Newcastle University - ongoing<br>PI for clinical trials sponsored by Italfarmaco, Edgewise, Pfizer, Dyne, Genethon, Roche – funding to Newcastle Hospitals NHS Foundation Trust - ongoing<br>Research Projects with Edgewise, Sarepta, Italfarmaco, Roche – funding through Newcastle University - ongoing |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry | **None** |

## Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the EAR.

### Table 2 Key issues

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Have comparators been appropriately specified in the submission? | Yes | The comparators are appropriate. Corticosteroids are part of the Standards of care for DMD and are intended to be given in association with givinostat. While vamorolone was not included as comparator, it is a corticosteroid which is expected to have similar indication and efficacy to classic corticosteroids (prednisolone and deflazacort), and therefore the specified comparators remain appropriate. I agree with the EAG opinion that following NICE approval vamorolone will be introduce in clinical practice as alternative to prednisolone and deflazacort, with younger boys starting corticosteroids being more likely prescribed with vamorolone while a smaller number of patients will switch from classic corticosteroids to vamorolone. Similarly to prednisolone and deflazacort, it is expected that givinostat will be prescribed in combination to (and not instead of) vamorlone (JAMA Neurol. 2022 Oct 1;79(10):1005-1014; JAMA Netw Open. 2022 Jan 4;5(1):e2144178) |
| Definition of ‘ambulant’ status and implications for generalisability to UK clinical practice | Yes | While it is noted the definition of “ambulant status” used in the clinical trials (inability to walk 10 meters in less than 30 seconds) slightly differs from the definition routinely used in clinical practice (inability to walk 10 meters), the definition is considered appropriate, clinically meaningful and reflective of clinical practice. The criteria used in the trials (10 meters in less than 30 seconds) can be |

| | | |
|---|---|---|
| | | described as “functional walk”, which has very similar meaning that the definition used in clinical practice. Moreover, the two definitions highly overlap - most patients requiring more than 30 seconds to walk 10 meters will refuse to perform the 10 meter walk/run test and will be classified as non-ambulant in UK clinical practice (Muscle Nerve, 2018 Nov;58(5):614-617.) |
| Post-hoc selection of givinostat OLE patients | Yes | I agree that all groups should be included in the analysis, although this will not completely resolve the bias. The three groups in fact are different for uncontrolled factors: the delayed group was randomized at the beginning of the study and systematically started treatment 18 months later, differently to the naïve group, which was not randomized and started givinostat at different timepoints. The delayed group was monitored according to the study protocol, similarly to the givinostat group but differently to the naïve group.<br>It is however important to note that the delayed LOA reported in the delayed group can not be explained from a scientific point of view as early treatment is expected to have the greater benefit based on the mechanism of action of givinostat |
| Source of data to inform comparative treatment efficacy | Yes | It is recognised that any external natural history comparator has limitation and risk of unbalance. With the specific issues raised, however<br>- The CINRG cohort is an older cohort, from international centres, mainly in the US and therefore might differ in term of standards of care compared to the more up to date UK Registry cohort. The impact of standards of care on clinical outcomes should be recognised<br>- The additional baseline prognostic factors offered by the CINRG cohort are not necessarily clinically relevant – the age of diagnosis more reflect that diagnostic process and awareness in individual countries/centres than describe the disease itself. While there are some suggestions that deflazacort is associated with better long term clinical outcomes compared to prednisone/prednisolone, this finding has not been confirmed by other long term patient cohort studies (J Neurol Neurosurg Psychiatry. 2025 Feb 12:jnnp-2024-335223; JAMA. 2022 Apr 19;327(15):1456-1468). Moreover, the effect of different steroid regimens more than type on clinical outcome |

| | | |
|---|---|---|
| | | is known and under-estimated in some of the long term patients cohort studies due to lack of information about corticosteroid regime (JAMA. 2022 Apr 19;327(15):1456-1468)<br>- The age of corticosteroid initiation has been shown to correlate with clinical outcomes (Neurology. 2024 May 28;102(10):e209206)<br>Therefore the UK registry cohort can be consider a valid and appropriate source of data, with the consideration however that the OLE data only include patients treated with corticosteroids while the UK Registry also include corticosteroid naïve patients. It might be relevant to repeat the analysis only including the steroid treated patients from the UK registry.<br>To confirm that validity of the data source, clinical milestones highly overlap with the data from another UK large adult patient cohort, with differences only in the age of NIV, which might be later compared to the reported 16 years (Eur J Neurol. 2024 Jun;31(6):e16267) |
| Impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints | Yes | There are inevitably limitations in the absence of randomised comparators however the specified milestones predictions reflect clinical experience as reported in other large UK patient cohorts (Eur J Neurol. 2024 Jun;31(6):e16267) with only a slight difference in the age of starting NIV, which might occur later compared to the suggested model, especially in steroid treated patients (Eur J Neurol. 2024 Jun;31(6):e16267). There are several evidence supporting a correlation between age of LOA and subsequent milestones (in particular respiratory milestones and scoliosis) |
| Use of 1.5% discounting | No | Not my area of expertise |
| Overestimation of caregiver utility impact | No | Not my area of expertise |

## Additional issues

**All:** Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

**Table 3 Additional issues from the EAR**

| Issue from the EAR | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|
| Additional issue 1: Insert additional issue | Please indicate the section(s) of the EAR that discuss this issue | Yes/No | Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making |
| Additional issue 2: Insert additional issue | Please indicate the section(s) of the EAR that discuss this issue | Yes/No | Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making |
| Additional issue N: Insert additional issue | | | [INSERT / DELETE ROWS AS REQUIRED] |

## Summary of changes to the company's cost-effectiveness estimate(s)

**Company only:** If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

**Table 4 Changes to the company's cost-effectiveness estimate**

| Key issue(s) in the EAR that the change relates to | Company's base case before technical engagement | Change(s) made in response to technical engagement | Impact on the company's base-case incremental cost-effectiveness ratio (ICER) |
|---|---|---|---|
| Insert key issue number and title as described in the EAR | Briefly describe the company's original preferred assumption or analysis | Briefly describe the change(s) made in response to the EAR | Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER. |
| Insert key issue number and title as described in the EAR | … | … | [INSERT / DELETE ROWS AS REQUIRED] |
| Company's base case following technical engagement (or revised base case) | Incremental QALYs: [QQQ] | Incremental costs: [£££] | Please provide company revised base-case ICER |

**Sensitivity analyses around revised base case**
PLEASE DESCRIBE HERE

# EAG addendum: review of company's response to technical engagement

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]: A Single Technology Appraisal


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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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**Contributions of authors to addendum**
CLM, ET, DC, and HP critiqued the clinical effectiveness. CC critiqued the literature searches and systematic literature reviews submitted in the company submission. HP and HT critiqued the statistical aspects of the submission. AS and HT critiqued the health economic analysis submitted by the company. AS, CLM, ET, DC, HP, and HT were involved in drafting and commenting on the addendum to the main EAG report.

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# Abbreviations

| Abbreviation | Definition |
|---|---|
| 1L | One litre |
| 4SC | Four Stair Climb |
| 6MWT | Six-Minute Walking Test |
| AE | Adverse Event |
| AFT | Acceleration Factor |
| AIC | Akaike Information Criterion |
| BMI | Body Mass Index |
| BNF | British National Formulary |
| BSA | Body Surface Area |
| BOI | Burden of Illness |
| CI | Confidence Interval |
| CINRG | Cooperative International Neuromuscular Research Group |
| CRD | Centre for Reviews and Dissemination |
| CRO | Contract Research Organisation |
| CS | Company Submission |
| DCO | Data Cut-Off |
| DMD | Duchenne Muscular Dystrophy |
| DNHS | Duchenne Natural History Study (DNHS) |
| EAG | Evidence Assessment Group |
| ECG | Electrocardiogram |
| ECM | Established Clinical Management |
| ECRF | Electronic Case Report Form |
| EK | Egen Klassifikation |
| EMA | European Medicines Agency |
| EQ-5D-5L | EuroQol 5 dimensions (standardised instrument for use as a measure of health outcome |
| ESS | Effective Sample Size |
| FEV | Forced Expiratory Volume |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| HHM | Hand Held Myometry |
| HR | Hazard Ratio |
| HRQoL | Health-Related Quality of Life |
| HST | Highly Specialised Technology |
| HTMF | Hand-to-mouth Function |
| HTA | Health Technology Assessment |
| HUI | Health Utilities Index |
| ICER | Incremental Cost Effectiveness Ratio |
| ICMJE | International Committee of Medical Journal Editors |
| IPD | Individual Participant Data |
| IQR | Inter Quartile Range |
| ITC | Indirect Treatment Comparison |
| ITT | Intention To Treat |
| KM | Kaplan-Meier |
| LOA | Loss of Ambulation |
| LYG | Life Year Gained |
| MAIC | Matched-Adjusted Indirect Comparison |
| MFMS | Motor Function Measure Scale |

| | |
|---|---|
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MMF | Mycophenolate Mofetil |
| MRS | Magnetic resonance spectroscopy |
| NE | Not evaluable |
| NHM | Natural History Model |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NI | No Information |
| NIV | Non-invasive Ventilation |
| NR | Not Reported |
| NSAA | North Star Ambulatory Assessment |
| OLE | Open-Label Extension |
| PedsQL | Pediatric Quality of Life Inventory |
| PEF | Peak Expiratory Flow |
| PODCI | Paediatric Outcomes Data Collection Instrument |
| PSM | Propensity Score Matching |
| PUL | Performance of Upper Limb |
| PSS | Personal Social Services |
| PY | Probably Yes |
| PN | Probably No |
| QA | Quality Assurance |
| QALY | Quality-Adjusted Life Year |
| RCT | Randomised Controlled Trial |
| REF | Research Excellence Framework |
| RoB2 | Risk of Bias 2 tool |
| ROBINS-I | Risk of bias in non-randomized studies of interventions |
| ROBIS | Risk Of Bias In Systematic reviews |
| RWE | Real-World Evidence |
| SAE | Serious Adverse Event |
| SAS | Safety Analysis Set |
| SD | Standard Deviation |
| SE | Standard Error |
| SF | Short Form Health Survey |
| SLR | Systematic Literature Review |
| SOP | Standard Operating Procedure |
| SPC | Summary of Product Characteristics |
| STA | Single Technology Appraisal |
| TAG | Technology Assessment Group |
| TEAE | Treatment Emergent Adverse Event |
| TSD | Technical Support Document |
| TTO | Time Trade-Off |
| UITC | Unanchored Indirect Treatment Comparison |
| UK | United Kingdom |
| US | United States |
| VLFF | Vastus Lateralis Fat Fraction |

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# 1. Overview of EAG report addendum

This addendum to the Evidence Assessment Group (EAG) report presents the EAG's critique of the additional evidence provided by the company in their Technical Engagement response to a number of key issues that were raised by the EAG in its report.

The addendum addresses the Key Issues for which additional evidence was provided by the company in the Technical Engagement response document and reports the EAG's revised base case. Where a Key Issue is of direct importance for the revised base case, the EAG's response has also been included in the Addendum.

# 2. Description and critique of additional evidence

The EAG's point by point response to the company's technical engagement submission is provided in the EAG Response to Technical Engagement response form. This Addendum to the EAG report focuses on the Key Issues for which the company has provided additional evidence or analyses during Technical Engagement and/or which impact the revised EAG base case, presented in Section 4. Addendum Table 1 summarises the Key Issues from the EAG report and whether new evidence was submitted by the company at Technical Engagement.

**Table 1: Summary EAG of key issues and new evidence**

| ID6323 | Summary of issue | New evidence? | Addendum section |
|---|---|---|---|
| Error! Reference source not found. | Have comparators been appropriately specified in the submission? | No | - |
| Error! Reference source not found. | Definition of 'ambulant' status and implications for generalisability to UK clinical practice | No | - |
| **Key Issue 3** | Post-hoc selection of givinostat OLE patients | Yes**Error! Reference source not found.** | 2.1 |
| Error! Reference source not found. | Source of data to inform comparative treatment efficacy | Yes**Error! Reference source not found.** | 2.2 |
| Error! Reference source not found. | What is the impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints? | Yes | 2.3 |
| Error! Reference | Use of 1.5% discounting | Yes**Error! Reference** | 2.4 |

| | | | |
|---|---|---|---|
| source not found. | | **source not found.** | |
| **Key Issue 7** | Overestimation of caregiver utility impact | Yes | 2.5 |
| Error! Reference source not found. | Costs and quality of life assumed the same in the full ventilation states and night ventilation states | No | 2.6 |
| Error! Reference source not found. | Overestimation by NHM of survival and DMD clinical progression events | No | - |
| Error! Reference source not found. | Mismatch of HERCULES NHM and available RCT data on givinostat | No | - |
| Error! Reference source not found. | Implementation of treatment effect within the economic model | No | 2.7 |

## 2.1. Key Issue 3: Post-hoc selection of givinostat patients from OLE study

In Key Issue 3, the EAG noted that the givinostat patients included in the company's economic model were only a subset of those in the OLE, selected post hoc. In response to this, at Technical Engagement, the company provided a sensitivity analysis to their base-case that includes all patients included in the OLE, rather than a subset of these participants (see pages 3-13 of EAG TE Response Form). This included an additional 58 participants in the delayed givinostat group who had been previously randomised to placebo in EPIDYS. The company provided updated Kaplan-Meier plots and uITC results, using the full OLE population.

Both the adjusted and unadjusted median time-to-event for each of the three outcomes for givinostat was substantially lower in the sensitivity analysis that included all patients in the OLE, compared to the subset (Addendum Table 2).

The company argue that randomisation to placebo followed by givinostat may introduce confounding, due to disease progression or accumulated morbidity. Whilst the EAG do not rule out the possibility of this, there is no evidence of a different treatment effect between Givinostat and Delayed Givinostat in CS Figure 27 (EAG report, Figure 3), with the Kaplan Meier curves showing remarkably similar results. In fact, it is the naïve givinostat group that likely has different characteristics to patients enrolled from EPIDYS, given that these participants have an earlier stage of disease and less time since initiation of corticosteroids. This group shows more evidence of confounding, given that the Kaplan-Meier plot for this group differs from the givinostat and delayed givinostat group. The EAG believe that the post-hoc selection of these participants clearly does favour givinostat, although the impact

on results is fairly minimal (due to the post-hoc selected participants being relatively few in number).

The EAG continues to believe that the post-hoc selection potentially introduces selection bias. However, due to the relatively minor impact on results and given that the sensitivity analysis has not been provided weighted to the EAG's preferred source of data for ECM (CINRG DHNS), the EAG does not include it in their updated base-case.

**Table 2: Median time-to-event for each outcome for unadjusted givinostat participants in both the company's base-case (a subset of OLE participants) and the sensitivity analysis that includes all patients who were included in the OLE**

| | Age at LOA | Age at NIV | Age at FVC <1L |
|---|---|---|---|
| **Company base-case (subset of OLE participants)** | 17.97 (15.40, NE) | 27.00 (27.14 to NE) | 34.90 (29.91, NE) |
| **Sensitivity analysis (all participants included in OLE)** | 17.25 (15.40, NE) | 25.92 (23.14, NE) | 33.50 (29.91, NE) |

## 2.2. Key Issue 4: What is the most appropriate source of data to inform comparative treatment efficacy?

Key Issue 4 arises due to the source of evidence used to inform ECM patients in the uITC when estimating comparative treatment efficacy.

The company argue that the most appropriate source of evidence is the UK registry study. At technical engagement they have provided the same justification for this as in their original submission but have provided more details regarding study characteristics to support their argument. They highlight the relevance of the UK registry for decision-making in a UK population. They also highlight the greater temporal alignment with EPIDYS/OLE from using the UK registry data source, given that it is collected more recently, which the EAG do accept as an argument. The geographical region may also align slightly better between EPIDYS/OLE and the UK registry than with CINRG DHNS, though overlap with either ECM data source is likely to be relatively poor with regards to geographical region.

The EAG agree that the UK registry should be used to inform the natural history baseline, given its relevance for decision-making a UK population. However, for estimating comparative treatment efficacy by matching to EPIDYS/OLE (the unanchored ITC), this source of evidence is poorly aligned.

The UK registry study does not report key prognostic factors that it would be critical to balance for the unanchored ITC to be valid, such as age at diagnosis and proportion of patients on deflazacort (among many others). Unlike in the UK registry study, these two prognostic factors are reported in CINRG DNHS. Whilst matching on these factors

substantially reduces the Effective Sample Size (ESS), *it is because of the ability to match on these additional prognostic factors that the ESS is reduced*.

The ESS is a statistical indicator of the degree of overlap. However, it is highly related to the number of prognostic factors used in matching. The lesser reduction in ESS when matching to the UK registry study rather than CINRG DHNS is not suggestive of good overlap, but simply that *there is not observed data on those prognostic factors to assess the degree of overlap*.

The EAG therefore do not believe that matching trial data to either of these observational evidence sources is likely to be robust but, given the limitations of both, the EAG continues to believe that the CINRG DHNS dataset is likely to more closely match EPIDYS/OLE due to the greater potential to match on observed prognostic factors known to be important. The EAG acknowledge that there are arguments for and against both data sources but also feel the need to highlight the substantial differences in results from using either data source over the other, and the inherent uncertainty from an unbalanced observational comparison. The HR for age at LOA used for the EAG's base-case is therefore that given in Addendum Table 3.

**Table 3: Summary of age at LOA MAIC used in the EAG's base-case: givinostat (EPIDYS/OLE) vs. ECM (CINRG DHNS)**

| Treatment | Median age at LOA (95% CI) | Givinostat vs. ECM HR for age at LOA (95% CI) |
|---|---|---|
| Givinostat unadjusted (EPIDYS / OLE study) | 17.97 (15.40, NE) | 0.346 (0.245, 0.488) |
| Givinostat weighted (EPIDYS / OLE study) | 16.49 (13.67, NE) | Robust SE: 0.469 (0.257, 0.855) |
| ECM (CINRG DHNS) | 13.01 (12.01, 14.00) | Comparator |

## 2.3. Key Issue 5: What is the impact of bias arising from the lack of randomised comparisons for key outcomes at longer-term timepoints?

Key Issue 5 relates to the lack of randomised comparisons for longer-term outcomes (age at LOA, age at NIV and age at FVC <1L) that inform the economic model. The follow-up of the randomised EPIDYS is too short to collect these, and the company have therefore use data from the givinostat OLE patients matched to an observational data source for ECM. Although they highlighted the potential uncertainties of such an approach, the EAG had suggested developing/identifying a surrogate relationship between the randomised outcomes collected in EPIDYS and the longer-term outcomes collected in the OLE.

The company have again highlighted the challenges in collecting longer-term data important to the economic model from a randomised trial in such a rare disease. They have also explained the lack of appropriately validated surrogate relationships in this population but

have provided additional information from published studies that supports the relationship short-term (randomised) outcomes and longer-term outcomes.

The EAG appreciates this additional information and acknowledge that there is a clear relationship/correlation between these different outcomes. The EAG do not dispute that the randomised findings in EPIDYS suggest a clinically meaningful effect. However, understanding the *magnitude* of efficacy of givinostat on those outcomes is critical to estimating the cost-effectiveness of givinostat, and this is highly uncertain.

The company have also performed a calculation that explores the relationship between 10MWT and LOA by applying an odds ratio calculated from Mazzone et al (2013)[1] for the relationship between 10MWT $\leqslant$7 seconds and the risk of LOA within 24 months follow-up. Note that in this calculation, the Mazzone OR is only applied to the ECM arm in EPIDYS to demonstrate that this provides a lower risk of LOA in ECM patients than would be predicted by the cost-effectiveness model. However, the same calculation is not applied to givinostat patients in EPIDYS, so it is not possible to directly assess what impacts using the Mazzone OR would have on EPIDYS data in a fair and balanced way.

If the company were to provide estimates in which they apply the same calculation to the givinostat patients in EPIDYS then this comparison might be more informative. As it currently is implemented, the calculation simply demonstrates that, using the Mazzone OR (for predicting LOA from 10MWT) underpredicts the age at LOA versus the model. It may do that in both arms (which in fact may therefore suggest that the model is overpredicting the age at LOA more generally).

The company also provides further evidence (from Arora et al. 2018[2] and Duong et al 2021[3]) that 10MWT and 4SC are strongly predictive of LOA. However, if this is the case then it suggests that an alternative approach that uses randomised data from EPIDYS to predict age at LOA may be of additional benefit to inform decision-making.

By using a non-randomised comparison (unanchored ITC) to inform the long-term outcomes, this potentially introduces significant bias compared to if randomised evidence was available on long-term outcomes. Whilst the EAG acknowledge that the challenges in collecting randomised efficacy data on long-term outcomes are inherent to the disease area, and that using short-term randomised outcomes to predict long-term outcomes may also introduce uncertainty, this does not resolve the potential bias that arises from the use of a non-randomised comparison that is likely to be unbalanced in prognostic factors.

Furthermore, upon considering the evidence provided during technical engagement, the EAG have also further refined their view on the use of acceleration factors to estimate outcomes at longer-term timepoints in the clinical evidence, where randomised data is not available. The EAG had previously stated in their report that, whilst the way the HRs and treatment effect were applied in the economic model did not align with the company's belief regarding

the treatment effect, the clinical evidence for longer-term outcomes for givinostat (calculated using AFs) did still align with a treatment effect only applied to age at LOA:

*"When analysed independently it is therefore reasonable (albeit with the extensive limitations detailed in Section 3.4) to assume the use of acceleration factors in this way. However, the HRs estimated for each of the outcomes capture exactly the same mechanism for the treatment effect due to the way in which they are derived (from age at LOA in givinostat patients, using acceleration factors)."*

However, having given further thought to the issue, the EAG consider that the treatment effect is also inappropriately applied in the clinical evidence due to the use of acceleration factors, and that Kaplan-Meier data, median time-to-event and HRs for age at NIV and age at FVC <1L will overestimate the efficacy of givinostat.

This is because by multiplying the time-to-event benefit from delaying age at LOA by a fixed ratio (i.e. applying an AF), it leads to a proportional increase in the age at later outcomes (NIV and FVC<1L). To align with the company's belief regarding the treatment effect, the difference between givinostat age at LOA and ECM age at LOA, should be *added to* the age at NIV and age at FVC<1L for ECM to estimate the age at NIV and age at FVC<1L for givinostat.

### 2.4. Key Issue 6: Use of 1.5% discounting

The company argue for a 1.5% discount rate to health outcomes (i.e., QALYs and not costs) from year 30 onwards. The NICE Methods Manual specifies that non-reference-case discounting can be applied only if the following three conditions are met:

i. The technology is for people who would otherwise die or have a very severely impaired life.
ii. It is likely to restore them to full or near-full health.
iii. The benefits are likely to be sustained over a very long period.

The company claim that givinostat meets two of the three criteria for applying non-reference discounting, as outline in the NICE Methods Manual. Firstly, that it is for a condition that severely impairs quality of life and is expected to deliver sustained benefits. The basis for the latter is the company's claim of robust evidence from both the 18-month randomised EPIDYS trial and its OLE, together comprising one of the longest clinical follow-up periods for any investigational therapy in DMD. The company highlight feedback from clinical advisers that the delay in LOA observed for givinostat in the OLE will have an impact on the overall progression of the disease in the non-ambulatory health states. The company further claim that applying the 1.5% discount rate across the full-time horizon may be more relevant.

The EAG do not agree that new evidence has been provided in the Technical Engagement response document to address Key Issue 6.

The EAG accepts that DMD severely impacts quality of life and thus meets the first criterion. However, the company has not provided any evidence for the second criteria, and the EAG views that provided for the third to be limited. The randomised period of EPIDYS was only 18 months and the OLE only 1204.2 days (i.e., about 3.3 years) while the model time horizon is lifetime for patients initially aged 6 years old, and the company is arguing for 1.5% discounting after 30 years. The EAG therefore maintains that non-reference-case discounting is not justified, and the base case discounting should remain 3.5%.

## 2.5. Key Issue 7: Overestimation of caregiver utility impact

The caregiver utility issue is influenced by a number of factors within the economic model:

### *i. The source of the utility values used*

The caregiver utility values used in the company economic model are presented in Addendum Table 4 (as Vignette study, ID6323).Table 4 As discussed in section 4.2.7 of the main EAG report, the EAG find insufficient evidence to support use of the vignette study and note the availability of alternatives such as the BOI study[7] values supplemented with the Landfeldt[4] values for health states 5, 6 and 7, as used in TA301. The EAG model the caregiver utility values on the EQ-5D-3L reported by Landfeldt et al. These utility values are also presented in Addendum Table 4.

**Table 4: Caregiver utility values used in appraisals of DMD**

| Health state | Landfeldt 2017[4] | BOI study (Evans et al[7]) | Vignette study (ID6323) |
|---|---|---|---|
| 1 - Early ambulatory | 0.85 | 0.55 | 0.72 |
| 2 - Late ambulatory | 0.83 | 0.41 | 0.67 |
| 3 - Transfer | | 0.48 | 0.58 |
| 4 - HTMF, no ventilation | 0.77 | 0.63 | 0.56 |
| 5 - No HTMF, no ventilation | | *NA* | 0.5 |
| 6 - HTMF, night-time ventilation | | *NA* | 0.54 |
| 7 - No HTMF, night-time ventilation | 0.79 | *NA* | 0.51 |
| 8 - Full time ventilation | | 0.36 | 0.48 |

### *ii. Methods for calculating the utility increments / decrements*

The EAG's method is to calculate the caregiver utility decrements relative to the utility values for carers in the least severe state is a common method in appraisals of this disease area and was selected by the committee in TA1031. The company's caregiver utility decrements / increments are calculated relative to healthy individuals in the general population (0.923) and are therefore substantially larger than the EAG's base case. The EAG's base case uses the utility decrements from the Landfeldt study[4] as reproduced in Addendum Table 5.

### *iii. Methods for accruing quality of life for carers*

The company's preferred method for accruing the carer quality of life is relative to midway health state. This involves rescaling the utility decrements in Addendum Table 5 to increments/ decrements in Addendum Table 6. The rescaled values are then applied to the incremental life years (givinostat minus ECM) in each cycle of the model. The EAG finds the choice of midway health state to be subjective and not backed by evidence. The method is novel, but the EAG prefer the more commonly applied disutilities method to modelling the carer quality of life presented in Table 5. Details of this issue, with a comparison of both methods, are presented in section 4.2.7 of the main EAG report.

### *iii. The number of caregivers*

The company assumes that the number of caregivers is constant at two, but the EAG prefers to model the increasing burden of care by modelling one caregiver for health states 1-3, increasing to two caregivers for health states 4-8.

**Table 5: Caregiver disutilities, EAG's values in comparison to company's values, using the disutilities method**

| Health state | Landfeldt (EAG - ID6323) | Landfeldt (Company scenario - ID6323) | Vignette study (Company base case - ID6323) |
|---|---|---|---|
| General population | NA | 0.000 | 0.000 |
| 1 - Early ambulatory | 0.00 | -0.065 | -0.203 |
| 2 - Late ambulatory | -0.02 | -0.084 | -0.253 |
| 3 - Transfer | -0.08 | -0.084 | -0.343 |
| 4 - HTMF, no ventilation | -0.08 | -0.139 | -0.363 |
| 5 - No HTMF, no ventilation | -0.08 | -0.139 | -0.423 |
| 6 - HTMF, night-time ventilation | -0.08 | -0.148 | -0.383 |
| 7 - No HTMF, night-time ventilation | -0.06 | -0.148 | -0.413 |
| 8 - Full time ventilation | -0.06 | -0.149 | -0.443 |
| 9 - Death (bereavement - all deaths) | NA | -0.923 | -0.923 |

**Table 6: Caregiver utility increments and decrements as per the relative to midway health state method preferred by the company**

| Health state | Landfeldt[4] (Company Scenario - ID6323) | Vignette study (Company base case - ID6323) |
|---|---|---|
| General population | 0.139 | 0.363 |
| 1 - Early ambulatory | 0.07 | 0.16 |

| | | |
|---|---|---|
| 2 - Late ambulatory | 0.055 | 0.11 |
| 3 – Transfer | 0.055 | 0.02 |
| 4 - HTMF, no ventilation | 0 | 0 |
| 5 - No HTMF, no ventilation | 0 | -0.06 |
| 6 - HTMF, night-time ventilation | -0.009 | -0.02 |
| 7 - No HTMF, night-time ventilation | -0.009 | -0.05 |
| 8 - Full time ventilation | -0.01 | -0.08 |
| 9 - Death (bereavement - all deaths) | -0.784 | -0.56 |

#### *iv. Application of the utility values in the death state.*

The company assumes that there is a utility benefit from extended survival due to treatment with givinostat. This benefit is achieved by combining the method of modelling caregiver QoL relative to the mid-way health state along with the assumption that two caregivers are required in health state 9 (the death state).

With regards to the extended survival benefit, the EAG notes a survival benefit of treating patients with DMD could be modelled as a treatment effect, taking into account available clinical evidence on the difference in survival between givinostat and ECM groups. However, such comparative evidence was not made available and therefore the EAG consider the survival benefit to be unsubstantiated. In support of their approach to modelling caregiver QALYs, the company refers to ongoing research on modelling caregiver QoL (CS, Doc B references 231 to 235). However, the EAG note that NICE guidance on appropriate methods has not yet been specified. The company also references a 2024 review of NICE submissions for disease-modifying therapies for multiple sclerosis, Alzheimer's disease, and spinal muscular atrophy which notes that the two main methods used to model carers' QoL are by attaching a carer utility or disutility to the patient's health state.[5]

Due to the lack of evidence supporting a survival benefit to caregiver's quality of life, the EAG prefers assigning zero carers in health state 9 and ascribing a disutility with the value of zero to the death state. Combined with the disutility approach to modelling caregiver QoL and using the disutility values from the Landfeldt et al study[4] this forms the EAG's base case.

### 2.6. Key Issue 8: Costs and quality of life assumed the same in the full ventilation states and night ventilation states

For utilities, the EAG preference is unchanged and the EAG base case continues to use the utilities from the BOI study. The BOI study was informed by Delphi panel measured quality of life for patients and caregivers in the UK using EQ-5D as part of Project HERCULES. The health state definitions align with those of the company model, including separate estimates for states 7 and 8.

The EAG agrees with the company that quantifying the costs of medical aids required by disabled patients at the more severe health states by using a multiplier was not robust and

thus no longer use it. The EAG agree with the company, costs derived from the Morgan et al. (2024)[6] are suitable for decision making, but caution they do not differentiate between states 7 and 8. These have been used in the model as presented in Addendum Table 7.

**Table 7: Direct medical costs without the multiplier applied for non-medical community services, aids, devices, and investments**

| Health states, N | Project HERCULES CPRD |
|---|---|
| Early ambulatory | £3,297.79 |
| Late ambulatory | £3,297.79 |
| 3 Transfer | £3,297.79 |
| 4 HTMF, no ventilation | £6,681.09 |
| 5 No HTMF, no ventilation | £6,681.09 |
| 6 HTMF, night ventilation | £9,842.74 |
| 7a No HTMF, 7b night ventilation | £9,842.74 |
| 8a, 8b Full ventilation | £9,842.74 |

## 2.7. Key Issue 11: Implementation of treatment effect within the economic model

*Company critique of EAG approach to including treatment effects in model*

The company did not present new evidence. The company instead explain their process for implementing treatment effects in the economic model. As age at NIV and age FVC <1L endpoints for givinostat were not reached within the clinical trial, they are estimated by applying acceleration factors from the UK registry study to age at LOA. This dependence on age at LOA is the company's argument against applying hazard ratios for LOA, NIV, and FVC <1L to the model transition probabilities as this would overestimate givinostat benefit. They also explain that the model includes more granular health state transitions than these outcomes. The company therefore uses a SOLVER-based approach to estimate HRs required to align median outcomes with those observed in the ITCs.

The company criticised the EAG's approach of applying treatment effect only to the transition from health state "(2) Late Ambulatory" to "(3) Transfer". They argued this underestimates the benefit of givinostat as it misses slowing of disease progression between ambulatory health states (e.g., between "(1) Early Ambulatory", "(2) Late Ambulatory" and between "(3) Transfer" and “(4) HTMF, no ventilation”).

To validate the company and EAG base case, the company estimate ratios for median age at key milestones using both models and compare to UK registry-derived acceleration factors. The company point out that the delay in LOA for givinostat has a disproportionately smaller impact on long-term outcomes compared to ECM in the EAG model.

The EAG reiterate that, if a treatment effect for givinostat versus ECM is only believed to impact age at LOA (as stated by the company in responses to clarification questions), then it should only be applied to states relating to ambulation in the economic model. Subsequent to LOA, patients discontinue givinostat, so it is clinically reasonable to assume that no additional treatment effect occurs beyond this point, and to model this as such.

### *Inappropriate assumptions when applying acceleration factors between givinostat and ECM*

The application of acceleration factors (AFs) to the givinostat data is inherently flawed:

- It actually *does* imply a treatment effect beyond LOA, even in the clinical evidence. This overestimates the efficacy of givinostat in the clinical evidence, and therefore also in the economic model (since the SOLVER HRs try to align the median age at endpoints to the clinical evidence).
- It assumes AFs between outcomes are unchanged by treatment effect. If givinostat is expected to have a treatment effect on age at LOA then this is not mathematically justifiable (a HR of >1 or <1 at age at LOA would imply that AFs between time-to-event endpoints would be different in givinostat compared to in ECM).

Within the clinical data on ECM, there are three endpoints that are reported and analysed:

- Age at Loss of Ambulation (LOA)
- Age at Non-Invasive Ventilation (NIV)
- Age at Forced Vital Capacity (FVC) <1L

However, since the endpoints are “age at…”, they inherently also include the previous timepoint. In fact, a more accurate way to think about these outcomes (in a way that more closely aligns to the economic model) is that they are comprised of time spent in 3 different health states. These could be considered as a weighted group of several of the Markov model states:

- Time in ambulatory (i.e., time in state 1 - Early ambulatory, state 2 - Late ambulatory, state 3 – Transfer)
- Time in non-ambulatory, no ventilatory support (defined as the difference between age at NIV and age at LOA) (i.e., time in state 4 - HTMF, no ventilation, state 5 - No HTMF, no ventilation)
- Time in non-ambulatory, invasive ventilation (defined as the difference between age at FVC <1L and age at NIV) (i.e., time in state 7a - No HTMF, night-time ventilation, state 8a - Full time ventilation, state 6 - HTMF, night-time ventilation, state 7b - No HTMF, night-time ventilation, state 8b - Full time ventilation)

To explain this in more detail, the EAG have created an illustrative diagram (Figure 1) to clarify this issue. In the Figure, the 3 endpoints are broken down into the 3 states they are each comprised of. For simplicity, the Figure 1 also assumes some easy numbers such that:

- ECM age at LOA = 10
- ECM age at NIV = 20
- ECM age at FVC <1L = 25

The company use AFs (calculated from the ECM data) to estimate the effects of givinostat on the different endpoints, given that there is no observed data on age at NIV and age at FVC <1L for givinostat. With the illustrative numbers in Figure 1, for ECM this therefore implies:

- An AF of 20/10 = 2 for Age at NIV versus Age at LOA
- An AF of 25/10 = 2.5 for Age at FVC <1L versus Age at LOA

Using results from the uITC, givinostat reduces the hazard of LOA compared to ECM. For illustrative purposes let's therefore assume that givinostat doubles the Age at LOA compared to ECM, such that it now equals 20. If the givinostat Age at LOA is then multiplied by the AFs estimated in ECM, the resulting time to each endpoint is effectively doubled. But what that means, if one looks at the time spent in each of the 3 states, is that they are *also* doubled.

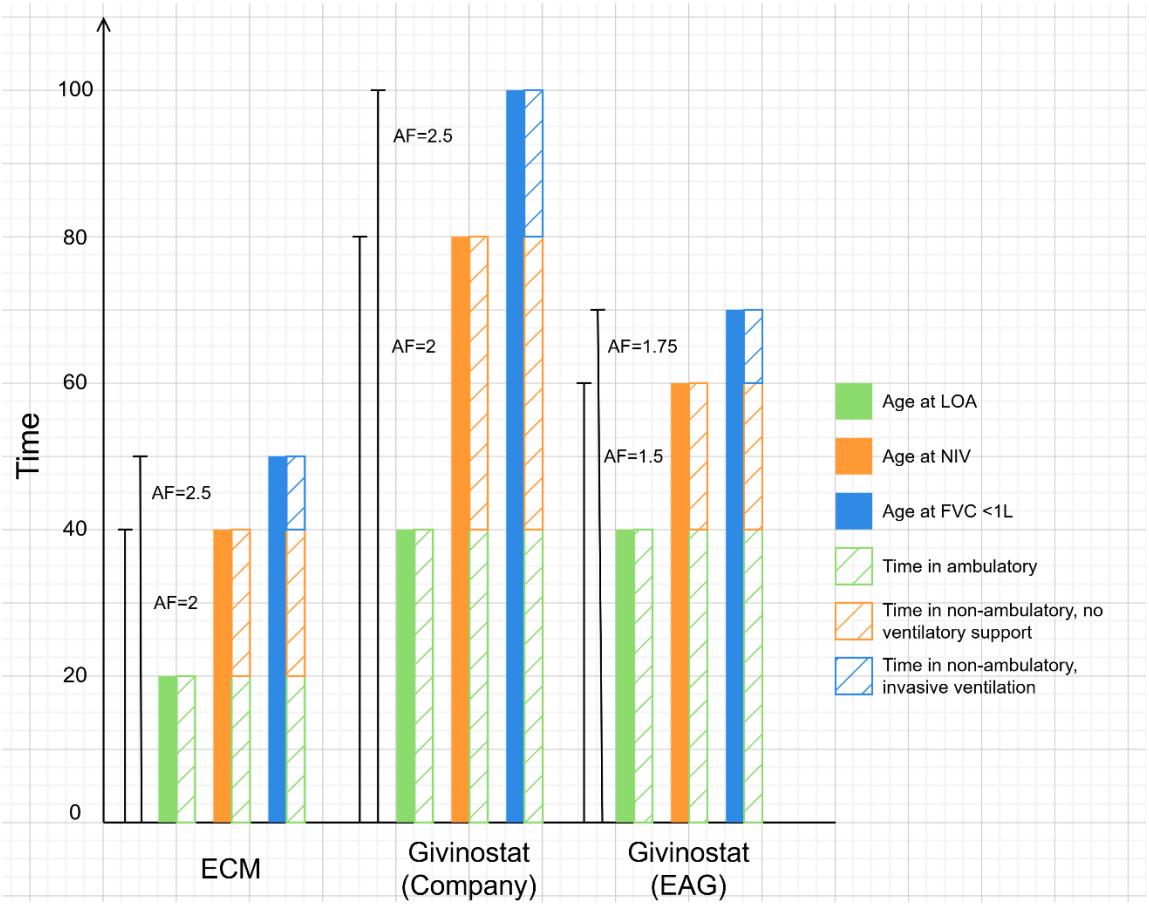



**Figure 1: Illustrative use of acceleration factors (AF) in estimating clinical effectiveness of longer-term outcomes**

This therefore implies (in the illustrative example) that givinostat doubles the time in ambulatory, and that it *also* doubles the time in in non-ambulatory, no ventilatory support and time in non-ambulatory, invasive ventilation. This contradicts with what one would clinically expect to be the case, given that givinostat is only administered whilst patients are ambulatory, and it also contradicts with what the company stated in response to clarification questions – that they only believe a treatment effect occurs during ambulation.

The EAG's view is that the endpoints should be modelled in a way that respects *where the treatment effect of givinostat is expected to be*. The correct way to estimate the later endpoints for givinostat would be:

- Age at NIV: model the increased Age at LOA (using the HR for LOA) on givinostat, and then add on the difference between Age at NIV and Age at LOA in the ECM patients
- Age at FVC <1L: model the increased Age at LOA (using the HR for LOA) on givinostat, and then add on the difference between Age at FVC <1L and Age at LOA in the ECM patients

This is effectively similar to what happens in the EAG's implementation of the Markov model in their cost-effectiveness analysis (see below).

Furthermore, the company's approach hugely overcomplicates the fitting of givinostat data, since (beyond the issues with the unanchored ITC discussed again in Addendum Sections 2.1 and 2.2) it requires:

- Applying AFs estimated in ECM to the givinostat KM data (this makes the implausible assumptions described above)
- Fitting survival distributions to extrapolate givinostat KM data to estimate median time-to-event (this adds an unnecessary layer of assumptions, when one could simply apply the AFs to the median age at LOA to get the median age at NIV and age at FVC<1L)
- Using SOLVER in Excel to solve for HRs that then seek to align a completely different natural history model to the weighted and extrapolated givinostat median time-to-event for each endpoint. This further assumes that the givinostat and ECM arms used *in the model* are balanced in prognostic factors (i.e. in addition to assuming prognostic factors are balanced between the UK registry data for ECM and the EPIDYS/OLE data for givinostat data).

### *EAG view on implementation of treatment effect in the model*

The EAG's proposed approach is simpler, makes fewer assumptions, and aligns with the company's stated belief as to where/when the treatment effect occurs. Transition probabilities to later states during ambulation (i.e. whilst on treatment) are reduced, so that patients progress through this part of the model more slowly. However, once they lose ambulation and progress to later states, they stop gaining any further benefit of Givinostat

and so the transitions between these later states remain the same between ECM and givinostat.

The company is correct in stating that the delay in LOA for givinostat has a disproportionately smaller impact on long-term outcomes compared to ECM in the EAG's base case, but this is exactly what one would expect to see if there was a proportional treatment effect applied to age at LOA only.

As Figure 1 shows, the EAG's implementation would still result in a marked increase in Age at LOA, Age at NIV and Age at FVC <1L in givinostat compared to ECM, but the increase is much less than the company's approach.

However, the transitions to which the EAG should apply the HR for age at LOA have been updated in the EAG's base-case model, to reflect all transitions where a treatment effect of givinostat versus ECM could be reasonably assumed to exist (i.e. whilst patients are still receiving givinostat). This applies to transitions 1 -> 2, 2 -> 3, and 3 -> 4, rather than just 2 -> 3. The effect of this is broadly similar to applying the HR to the full ambulatory Kaplan-Meier curve, rather than just the middle chunk of it. The HR used is as described in Addendum Table 3 in Section 2.2, specifically age at LOA HR of 0.469 (0.257, 0.855) with post-hoc selected givinostat matched to CINRG DHNS.

# 3. EAG response to additional issues raised at Technical Engagement

## 3.1. Additional issue 2: Givinostat hydrochloride versus givinostat free base case

In the revised base case, the EAG have incorporated the corrected Dose A, Dose B, and Dose C values from EPIDYS, and have updated using the 8.86 mg/mL concentration noted in Additional Issue 2 into the EAG base case.

## 3.2. Additional issue 3: Differences between trial and SmPC dosing

The company model applies the givinostat dosing regimen observed in the EPIDYS trial to ensure alignment with the source of efficacy data, with dose adjustments based on patient weight over time. The SmPC provides recommends a slightly higher dose so the model may underestimate benefit but the extent is unknown without further evidence. The EAG have now followed the company's base case dosing.

## 3.3. Additional issue 4: Wastage

In the revised base case, the EAG have followed the company position that wastage is negligible and have not incorporated in the base case.

### 3.4. Additional issue 6: Model starting age

The company responded to a query from NICE regarding starting the model at prevalent age of the EPIDYS trial (9.8 years in overall ITT population).

The company reasons that the age six starting age of the model is consistent with the SmPC for givinostat, which specifies use in boys aged six years and older. This starting age also aligns with the EPIDYS clinical trial, which enrolled boys aged at least 6 years. By modelling from age six, the population reflects the earliest point of trial eligibility and aligns with the intended treatment population in UK clinical practice. The company furthermore reasons that EPIDYS underestimates the treatment benefit due to its true mean age being older.

The EAG agrees that the starting age should be six, and agrees that EPIDYS may underestimate treatment benefit (though the extent is unknown).

## 4. EAG updated results

In Table 4 of the Technical Engagement response, the company outline changes made to their revised base case. This is outlined below as follows:

- An updated simple PAS of [redacted]% applied to the cost of givinostat which reduces the cost per 8.86 mg/mL 140 mL bottle from £13,846 to £[redacted].
- Givinostat monitoring costs: included as per EAG's base case accounting for differences between givinostat and ECM arms as described in section 4.2.8 of the EAG report.
- Givinostat dosing calculations: based on 8.86 mg/mL from 10 mg/mL, aligned with the bottle size and costing.
- Severity modifier: applied to incremental patient QALYs only where it previously was applied to patient and carer QALYs .

The revised company base case results (with updated PAS) are reported in Table 5 of the Technical Engagement response document. The company's probabilistic ICER is [redacted]. and the deterministic ICER is [redacted], where the original base case probabilistic ICERs was [redacted] and the deterministic ICER was [redacted]. These have been reproduced by the EAG for the incremental analysis in Addendum Table 9 and Table 10. Note the probabilistic results will not match, highlighting the uncertainty in the results.

Following technical engagement, the EAG has updated its preferred base-case. The EAG incorporates the updated PAS discount and the correction made to the dosing calculations. The EAG welcomes the company's correction to applying the severity modifier, as described in section 4.2.7 of the main EAG report, the severity modifier is applied only to the incremental patient QALYs. The EAG furthermore modifies the company's base case by adding the assumptions presented in Addendum Table 8. This summarises the scenarios and outlines changes from the EAG's original base case.

Results of the deterministic analysis incrementally applying these scenarios to the updated company base case are provided in Addendum Table 9 and probabilistic results are provided in Addendum Table 10.

### Table 8: EAG Preferred assumptions following technical engagement

| Scenario | Changed from previous base case? (Relevant Key Issue) |
|---|---|
| Scenario 1. 3.5% discounting of both costs and effects | No<br>(Key Issue 6) |
| Scenario 3. Include caregiver QALYs for ECM arm (the method for accruing the caregiver utilities) | No<br>(Key Issue 7) |
| Scenario 4. Change caregiver utility impact calculation (the source of the utility values used and the methods for calculating the utility increments / decrements) | Yes, caregiver utility decrements calculated from the utility values reported Landfeldt et al.[4]<br>(Key Issue 7) |
| Scenario 5. Changing the number of caregivers | No<br>(Key Issue 7) |
| Scenario 6. Utilities that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") | Yes<br>The EAG have adopted direct medical costs from the company's base case, the HERCULES CPRD study by Morgan et al without the multiplier applied to direct costs.<br>The EAG have kept the prior BOI source for utilities.<br>(Key Issue 8) |
| TE Scenario 1. Apply the age at LOA HR (0.469 (0.257, 0.855) with post-hoc selected givinostat matched to CINRG DHNS) to transitions 1->2, 2->3 and 3->4 rather than just 2->3. | Yes, previously applied HR to only transitions 2->3<br>(Key Issues 3 and 4 for the selected HR, Key Issue 11 for application to economic model) |

**Table 9: EAG preferred assumptions added incrementally to EAG base case (deterministic results)**

| Interventions | Total Costs | Total Patient QALYs | Total Carer QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|
| Company's base-case | | | | | | | |
| ECM | £99,448 | 6.14 | 0.00 | | | | |
| Givinostat | [redacted] | 10.15 | 9.18 | [redacted] | 4.00 | 15.98 | [redacted] |
| Company's base-case + EAG's preferred assumption S1: 3.5% discounting of both costs and effects | | | | | | | |
| ECM | £99,448 | 6.08 | 0.00 | | | | |
| Givinostat | [redacted] | 9.57 | 6.85 | [redacted] | 3.48 | 12.77 | [redacted] |
| Company's base-case + S1 + EAG's preferred assumption S3: Include caregiver QALYs for ECM arm | | | | | | | |
| ECM | £99,448 | 6.08 | -32.18 | | | | |
| Givinostat | [redacted] | 9.57 | -25.32 | [redacted] | 3.48 | 12.77 | [redacted] |
| Company's base-case + S1 + S3 + EAG's preferred assumption S4: Change caregiver utility impact calculation | | | | | | | |
| ECM | £99,448 | 6.08 | -1.35 | | | | |
| Givinostat | [redacted] | 9.57 | -1.65 | [redacted] | 3.48 | 5.62 | [redacted] |
| Company's base-case + S1 + S3 + S4 +EAG's preferred assumption S5: Changing the number of caregivers | | | | | | | |
| ECM | £99,448 | 6.08 | -1.25 | | | | |

| Interventions | Total Costs | Total Patient QALYs | Total Carer QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|
| Givinostat | [redacted] | 9.57 | -1.49 | [redacted] | 3.48 | 5.68 | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 +EAG's preferred assumption S6: Utilities that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") | | | | | | | |
| ECM | £99,448 | 7.36 | -1.25 | | | | |
| Givinostat | [redacted] | 10.62 | -1.49 | [redacted] | 3.26 | 3.67 | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 + EAG's TE Scenario 1: Applying the age at LOA HR 469 (0.257, 0.855) with post-hoc selected givinostat matched to CINRG DHNS) to transitions 1->2, 2->3 and 3->4 rather than just 2->3. | | | | | | | |
| ECM | £99,448 | 7.36 | -1.25 | | | | |
| Givinostat | [redacted] | 9.51 | -1.07 | [redacted] | 2.15 | 2.76 | [redacted] |

**Table 10: EAG preferred assumptions added incrementally to EAG base case (probabilistic results)**

| Interventions | Total Costs | Total Patient QALYs | Total Carer QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|
| Company's base-case | | | | | | | |
| ECM | £99,067 | 6.16 | 0.00 | | | | |
| Givinostat | [redacted] | 10.20 | 9.23 | [redacted] | 4.04 | 16.10 | [redacted] |
| Company's base-case + EAG's preferred assumption S1: 3.5% discounting of both costs and effects | | | | | | | |
| ECM | £99,321 | 6.10 | 0.00 | | | | |
| Givinostat | [redacted] | 9.60 | 6.86 | [redacted] | 3.50 | 12.81 | [redacted] |
| Company's base-case + S1 + EAG'spreferred assumption S3: Include caregiver QALYs for ECM arm | | | | | | | |
| ECM | £98,635 | 6.10 | -32.31 | | | | |
| Givinostat | [redacted] | 9.59 | -25.38 | [redacted] | 3.49 | 12.87 | [redacted] |
| Company's base-case + S1 + S3 + EAG's preferred assumption S4: Change caregiver utility impact calculation | | | | | | | |
| ECM | £98,851 | 6.10 | -1.40 | | | | |
| Givinostat | [redacted] | 9.55 | -1.68 | [redacted] | 3.46 | 5.59 | [redacted] |
| Company's base-case + S1 + S3 + S4 +EAG's preferred assumption S5: Changing the number of caregivers | | | | | | | |
| ECM | £98,849 | 6.08 | -1.31 | | | | |

| Interventions | Total Costs | Total Patient QALYs | Total Carer QALYs | Incremental Costs | Incremental Patient QALYs | Incremental QALYs (w/ severity Modifier) | ICER |
|---|---|---|---|---|---|---|---|
| Givinostat | [redacted] | 9.55 | -1.54 | [redacted] | 3.47 | 5.67 | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 +EAG's preferred assumption S6: Utilities that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation") | | | | | | | |
| ECM | £99,748 | 7.38 | -1.36 | | | | |
| Givinostat | [redacted] | 10.67 | -1.58 | [redacted] | 3.29 | 3.72 | [redacted] |
| Company's base-case + S1 + S3 + S4 + S5 + EAG's TE Scenario 1: Applying the age at LOA HR 0.469 (0.257, 0.855) with post-hoc selected givinostat matched to CINRG DHNS) to transitions 1->2, 2->3 and 3->4 rather than just 2->3. | | | | | | | |
| ECM | £98,714 | 7.36 | -1.15 | | | | |
| Givinostat | [redacted] | 9.60 | -0.95 | [redacted] | 2.24 | 2.89 | [redacted] |

# 5. References


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# Single Technology Appraisal

# Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

# Technical engagement response form

## Key issues for engagement

| Key issue | Does this response contain new evidence, data or analyses? | Company Response | EAG response |
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| 1. Have comparators been appropriately specified in the submission? | No | Yes, the comparator has been appropriately specified. Established clinical management (ECM) is the only relevant comparator to givinostat.<br>Ataluren is not an appropriate comparator for givinostat in this appraisal as it is used in a very small sub-population of patients with Duchenne muscular dystrophy (DMD) and its future use in the UK is very uncertain. The Evidence Assessment Group (EAG) agrees with this. The European Commission confirmed its decision not to renew the conditional marketing authorisation for ataluren in the European Union on 28 March 2025, as the effectiveness of the medicine had not been confirmed.[1]<br>While prednisone and deflazacort are included as comparators, vamorolone was not accepted or widely used at the time of scoping and was only approved during our submission process. Moreover, the efficacy of vamorolone remains uncertain – this was a key point of discussion during its ACM – and its impact on the natural history model for ECM, or when used in combination with givinostat, is unknown. Importantly, vamorolone would be used alongside givinostat rather than instead of it, meaning it would be included in both treatment arms. As a result, it is not displacing the use of givinostat in the treatment pathway, and its inclusion would likely have minimal impact on the relative treatment effect. The company expects that boys and young | As noted, the EAG and the company agree that ataluren is not an appropriate comparator for givinostat.<br>The outstanding issue relates to NICE's approval of vamorolone for DMD in January 2025 (TA1031), after the company submission for givinostat (04 December 2024). Vamorolone is a corticosteroid and, therefore, has the potential to displace prednisone/prednisolone or deflazacort as a component of ECM. Prednisolone is currently the most commonly prescribed steroid for DMD in the UK and is available as a generic version. TA1031 considered vamorolone to have a more favourable side effect profile than prednisone or deflazacort. The EAG's report also noted that TA1031 had expressed uncertainty regarding the clinical effectiveness of vamorolone compared to prednisone.<br>The EAG agree that inclusion of vamorolone is likely to have a minimal impact on relative treatment effect estimates. As vamorolone is newly approved, the EAG also agree that there are uncertainties and unknowns regarding the use of vamorolone in practice. However, vamorolone has a distinct adverse event profile, and different acquisition and administration costs to prednisone. Inclusion of vamorolone in the economic model may influence resource |

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| | | men initiating givinostat will continue receiving some form of systemic corticosteroid therapy, which may include prednisone, deflazacort, or vamorolone. | utilisation estimates and health state utility values. The EAG suggested scenario analyses relating to the use and probable market share of vamorolone in place of standard corticosteroids. |
| 2. Definition of 'ambulant' status and implications for generalisability to UK clinical practice | No | Loss of ambulation (LOA) is a gradual change that occurs over time, rather than a clear-cut binary outcome. Typically, boys increasingly lose the ability to mobilise, starting with impaired/loss of ability to run, hop, jump, rise from the floor and climb stairs – followed by needing assistance from other people or mobility aids to walk short distances. Boys transition gradually to wheelchair dependence – initially for longer distances only, and eventually all the time. This gradual progression and variation of ability within and between individuals means that there is no agreed definition of ambulatory status in DMD. However, specific definitions must be used within the constraints of clinical trial inclusion and exclusion criteria and assessment of outcomes. The definitions of ambulatory used in the givinostat studies fall within spectrum of definitions used in clinical practice, and clinical experts have confirmed that the definitions used are appropriate. These include the definition from North Star data collection forms, which define ambulant as being able to walk 10 metres without assistance (and non-ambulant as not being not able to walk 10 metres without assistance). Furthermore, the givinostat trials definitions align with that used in the long-term Phase 3 study of ataluren (Study 019) where LOA was defined as a boy consistently taking more than 30 seconds to run/walk 10 metres.[2]<br>In EPIDYS, LOA is defined as any boy/young man who satisfies both of the following criteria at the same visit at any point prior to or at the end of the study and continues to satisfy the criteria at all subsequent visits to the end of the study:<br>• Boy/young man is unable to perform the 6-minute walking test (6MWT) due to physical inability<br>• Boy/young man is unable to complete the 10-metre walk/run test (10MWT) in 30 seconds or less without any support or devices (10MWT grading ≤2).<br>Study 51 definition of non-ambulant boys/young men:<br>• Unable to complete the 10MWT in 30 seconds or less without any support or devices. | Thank you for providing further clarity of the definition of ambulant/ non-ambulant in the company studies. EAG understand that outcome measures and inclusion criteria in clinical trials tend to be focused and specific. Key Issue 2 considers what this means for use of givinostat in practice, in the UK. Key Issue 2 is not a critique of the internal validity of the company's trial but considers external validity (generalisability). The EAG also note that the company are seeking a NICE recommendation for givinostat for use in ambulant patients only, yet MHRA conditional marketing authorisation has been granted for both ambulant and non-ambulant patients. Therefore, the question of how clinicians will distinguish between ambulant and non-ambulant patients – and any uncertainty involved with that assessment - is pertinent to this appraisal.<br><br>Further, Key Issue 2 raised the uncertainty of how 'ambulant status' had been defined in the real world data set used to inform the ECM 'arm' for the MAIC. Key Issue 2 also noted that the impact of using different measures of ambulation or thresholds for ambulant/non-ambulant could also be considered in the company submission. This has not been addressed by the company in their response to Key Issue 2. The impact of how ambulant status is defined across the givinostat and ECM 'arms' in the MAIC are of importance for the estimation of treatment effect. See Key Issue 11 for discussion of the implementation of treatment effect within the economic model. |
| 3. *Post-hoc* selection of givinostat OLE patients | Yes | As described in Section B.2.8.1 of the CS and in Clarification Questions (CQ) A14, patients in the two givinostat studies were eligible to be included in the indirect treatment comparisons (ITCs) if they had received givinostat from study entry: | The EAG continues to believe that the post-hoc selection potentially introduces selection bias and argues that the sensitivity analysis OLE results conducted during Technical Engagement (including all patients in the OLE study) should be included in the base-case. The |

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| | | • Patients who were randomised to placebo in EPIDYS and who received delayed givinostat in the Open-label extension (OLE) study were excluded given the treatment effect in those patients would be confounded.<br>• Patients who were enrolled in Study 51 but were previously enrolled in Study 43 were excluded due to different inclusion and exclusion criteria and givinostat exposure in Study 43 and EPIDYS.<br>Patients enrolled in EPIDYS who went on to enrol in the OLE study were assessed based on their most recent follow-up to avoid double counting.<br>The EAG note that the *post hoc* selection of givinostat OLE patients is a key issue (Key Issue 3) and suggest a sensitivity analysis that includes all patients from the OLE in the ITCs to resolve this issue. In response to this key issue, we have conducted a sensitivity analysis that includes all patients in the OLE (including those originally enrolled in Study 43) in the ITCs.<br>Whilst these sensitivity analyses have been conducted in response to the EAG's request, the base case analysis, which includes only the givinostat and givinostat-naïve groups from the OLE, is the most robust. These patients met the trials' inclusion and exclusion criteria and received givinostat from baseline – i.e. at the point of initial eligibility. In contrast, patients in the delayed givinostat group also met the inclusion and exclusion criteria at trial entry but received placebo during the 18-month EPIDYS period before initiating givinostat in the OLE. Using the start of givinostat in the OLE as a new "baseline" does not eliminate the impact of disease progression or accumulated morbidity during the placebo period. Therefore, even though these patients technically meet the same criteria, they are not clinically equivalent to patients who started treatment at trial entry.<br>Furthermore, 61 patients were initially randomised to placebo in EPIDYS, but only 58 continued into the OLE (see Figure 2 of CQ responses), meaning the delayed givinostat group includes only those who remained eligible for treatment after 18 months. This introduces a selection bias, as patients had to remain eligible to receive givinostat in the OLE. As a result, this group may appear to respond better, not necessarily because of the treatment, but because only the healthier subset transitioned into the OLE. Including these patients risks underestimating the true treatment effect of givinostat due to their later and potentially less favourable starting point.<br>In addition, excluding the Study 43 patients enrolled in the OLE from the base-case ITC analysis was considered reasonable by the EAG, given the differences in inclusion criteria, baseline characteristics | Addendum to the EAG report gives a full discussion of the response (Section 2.1).<br><br>The company argue that randomisation to placebo followed by givinostat may introduce confounding, due to disease progression or accumulated morbidity. Whilst the EAG do not rule out the possibility of this, there is no evidence of a different treatment effect between Givinostat and Delayed Givinostat in CS Figure 27 with the Kaplan Meier curves showing remarkably similar results (included in main EAG report as Figure 3).<br><br>In fact, it is the naïve givinostat group that likely has different characteristics to patients enrolled from EPIDYS, given that these participants have an earlier stage of disease and less time since initiation of corticosteroids. This group shows more evidence of confounding, given that the Kaplan-Meier plot for this group differs from the givinostat and delayed givinostat group.<br><br>Furthermore, the post-hoc selection of these participants clearly does favour givinostat. The company's sensitivity analyses presented here illustrate this, although the impact on results is fairly minimal (due to the post-hoc selected participants being relatively few in number). A further argument for including all participants that were included in the OLE is due to the increased sample size (and statistical power) from doing so.<br><br>The EAG continues to believe that the post-hoc selection potentially introduces selection bias. However, due to the relatively minor impact on results and given that the sensitivity analysis has not been provided weighted to the EAG's preferred source of data for ECM (CINRG DHNS), the EAG does not include it in their updated base-case. |

indicating less progressed disease, and treatment dosing regimen for this study.

For these reasons, these analyses are presented as sensitivity analyses only. However, it is noted that the results show consistent significant benefit for givinostat compared with ECM for all endpoints.

Table A presents the givinostat (unadjusted and weighted) and ECM baseline characteristics for the conducted sensitivity analyses. In line with the original analyses, matching was based on age at start of CS treatment. The effective sample size (ESS) was 151.9, a reduction of around one-third compared with the original sample size of 224 givinostat patients, suggesting reasonable overlap in patient characteristics for age at start of CS treatment.

**Table A: Comparison of baseline characteristics: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**

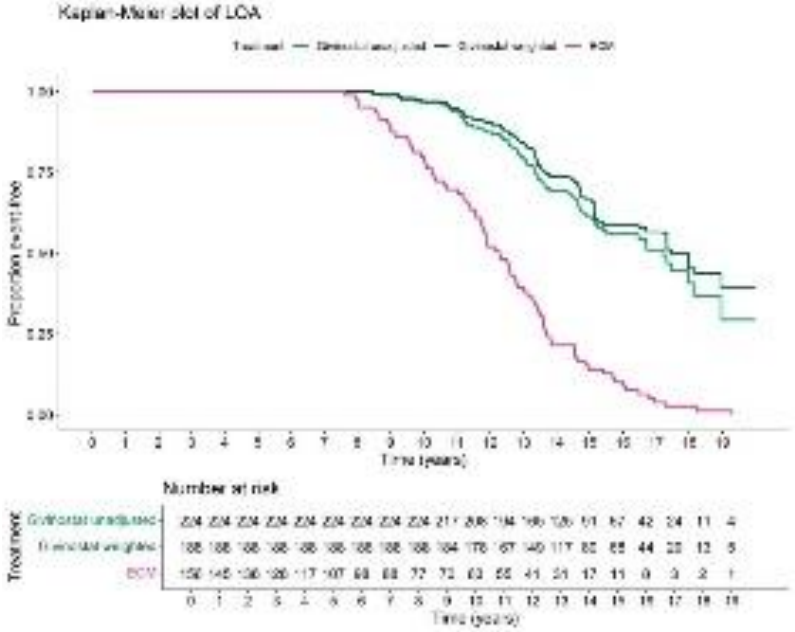
| Treatment arm | N/ESS | CS start age (years) |
|---|---|---|
| Givinostat unadjusted | 224.0 | 5.99 |
| Givinostat weighted | 151.9 | 7.20 |
| ECM | 156.0 | 7.20 |

Abbreviations: CS, corticosteroids; ECM, established clinical management; ESS, effective sample size.

**Age at loss of ambulation**

The Kaplan-Meier (KM) plots for age at LOA for givinostat patients for both unadjusted and weighted patient data, compared with patients receiving ECM (estimated using an acceleration factor) are presented in Figure A.

**Figure A: Kaplan-Meier plot for age at LOA MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**




Abbreviations: ECM, established clinical management; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; OLE, open-label extension; UK, United Kingdom.

Median age at LOA for givinostat treated patients was 17.3 years pre-weighting and 18.0 years post-weighting, compared with 12.3 years for ECM treated patients (Table B). Patients treated with givinostat were significantly older at LOA compared with patients treated with ECM, with HR (95% confidence interval [CI]) of 0.201 (0.142, 0.285) from the weighted comparison with robust SE (Table B). These results are consistent with the base case HR of 0.185 (95% CI 0.121, 0.282).

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|

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|---|---|---|---|---|---|
| Givinostat unadjusted (All patients) | 224.0 | 78 | 17.25 (15.40, NE) | **0.241 (0.176, 0.330)** |
| Givinostat weighted (All patients) | 151.9 | 63 | 17.97 (15.26, NE) | Robust SE: **0.201 (0.142, 0.285)** Bootstrap: **0.200 (0.154, 0.263)** |
| ECM (UK real-world data) | 156.0 | 79 | 12.28 (11.74, 13.13) | Comparator |

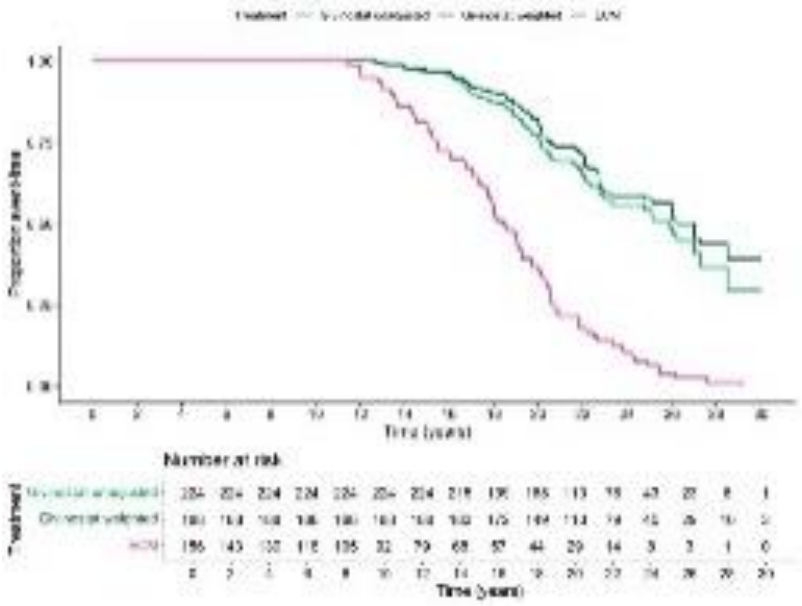
**Table B: Summary of age at LOA MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**

**Bold text** indicates a significant difference between treatments. Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.

**Age at non-invasive ventilation**

As described in Section B.2.8 of the CS, the estimated acceleration factor was applied to the age at LOA data for patients receiving givinostat. Based on this approach, KM curves estimating the age at NIV for both unadjusted and weighted givinostat patient data, compared with patients receiving ECM, are presented in Figure B.

**Figure B: Kaplan-Meier plot for age at NIV MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**




Abbreviations: ECM, established clinical management; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; UK, United Kingdom.

Median age at NIV for givinostat treated patients was 25.9 years pre-weighting and 27.0 post-weighting, compared with 18.5 years for ECM treated patients (Table C). Patients treated with givinostat were significantly older when receiving NIV, compared with patients treated with ECM with a HR (95% CI) of 0.206 (0.145, 0.293) from the weighted comparison with robust SE (Table C). These results are consistent with the base case HR (95% CI) of 0.190 (0.124, 0.290).

**Table C: Summary of age at NIV MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. EBM HR (95% CI) |
|---|---|---|---|---|

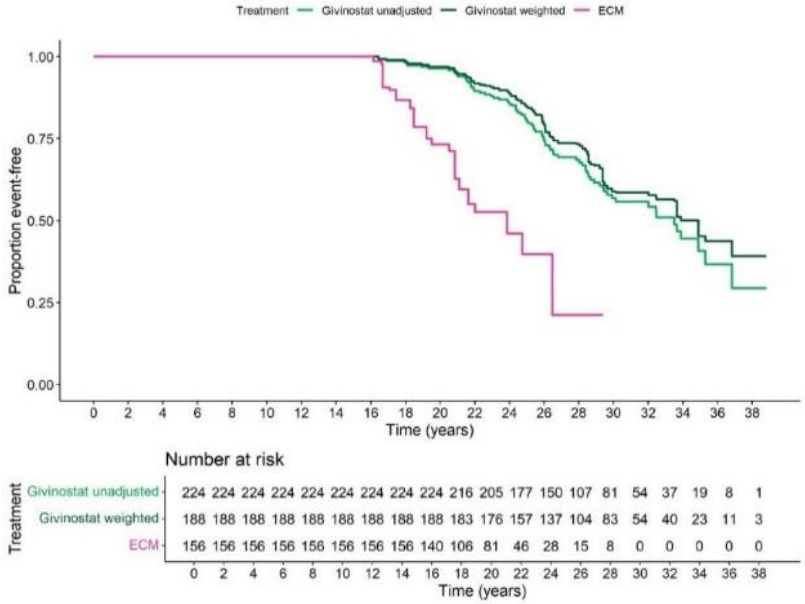
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|---|---|---|---|---|---|
| Givinostat unadjusted (All patients) | 224.0 | 78 | 25.92 (23.14, NE) | **0.247 (0.180, 0.338)** |
| Givinostat weighted (All patients) | 151.9 | 63 | 27.00 (22.93, NE) | Robust SE: **0.206 (0.145, 0.293)** Bootstrap: **0.206 (0.158, 0.270)** |
| ECM (UK real-world data) | 156.0 | 79 | 18.46 (17.76, 19.70) | Comparator |

**Bold text** indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; EBM, established clinical management; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; NIV, non-invasive ventilation; OLE, open-label extension; SE, standard error.

**Age at forced vital capacity <1L**

As described in Section B.2.8 of the CS, the estimated acceleration factor was applied to the age at LOA data for patients receiving givinostat. Based on this approach, KM curves estimating the age at FVC <1L for both the unadjusted and weighted givinostat patient data, compared with patients receiving ECM, are presented in Figure C.

**Figure C: Kaplan-Meier plot for age at FVC <1L MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**




Abbreviations: 1L, 1 litre; FVC, forced vital capacity; MAIC, matching-adjusted indirect comparison.

Median age at FVC <1L for givinostat treated patients was 33.5 years pre-weighting and 34.9 post-weighting, compared with 23.9 years for ECM treated patients (Table D). Patients treated with givinostat were significantly older when reaching FVC <1L compared with patients treated with ECM with a HR (95% CI) of 0.218 (0.149, 0.321) from the weighted comparison with robust SE (Table D). These results are consistent with the base case HR of 0.214 (0.139, 0.329).

**Table D: Summary of age at FVC <1L MAIC: givinostat (all patients) vs. ECM (UK real-world data) | Sensitivity analysis including all givinostat patients**

| Treatment (study) | N/ESS | Events | Median (95% CI) | Givinostat vs. ECM HR (95% CI) |
|---|---|---|---|---|
| Givinostat unadjusted (All patients) | 224.0 | 78 | 33.50 (29.91, NE) | **0.246 (0.173, 0.352)** |
| Givinostat weighted (All patients) | 151.9 | 63 | 34.90 (29.64, NE) | Robust SE: **0.218 (0.149, 0.321)** Bootstrap: **0.217 (0.169, 0.275)** |
| ECM (UK real-world data) | 156.0 | 67 | 23.86 (21.62, 26.47) | Comparator |

**Bold text** indicates a significant difference between treatments. Abbreviations: 1L, 1 litre; CI, confidence interval; ECM, established clinical management; ESS, effective sample size; FVC, forced vital capacity; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SE, standard error.

The impact of using the medians from the MAIC sensitivity analyses in the economic model is presented in the scenario analysis under the summary of changes to the cost-effectiveness results. This approach uses the SOLVER methodology as proposed by the Company – see response to Key Issue 11. This scenario is shown to have a limited impact on the updated base case ICER (-1.68%).

In addition, in response to EAG comments, the impact of including the standard deviation (SD) for age at CS initiation in the matching process was considered. The SDs were very similar before adjustment between givinostat and ECM (Table E).

**Table E: Comparison of baseline characteristics across base-case and sensitivity analyses: givinostat vs. ECM (UK real-world data) | Exploring including SD in analyses**

| Treatment arm | Model | N/ESS | CS start age (years) | CS start age SD (years) |
|---|---|---|---|---|
| Givinostat base-case | Unadjusted | 148 | 6.094 | 1.877 |
| Givinostat base-case | Adjusted | 105.1 | 7.197 | NA |
| Givinostat base-case with additional adjustment for SD | Adjusted | 108.2 | 7.197 | 1.896 |
| Givinostat all patients sensitivity analysis | Unadjusted | 224 | 5.991 | 1.910 |
| Givinostat all patients sensitivity analysis | Adjusted | 151.9 | 7.197 | NA |
| Givinostat all patients sensitivity analysis with additional adjustment for SD | Adjusted | 155.7 | 7.197 | 1.896 |
| ECM (UK real-world data) | Unadjusted | 156 | 7.197 | 1.896 |

Abbreviations: CS, corticosteroids; ECM, established clinical management; ESS, effective sample size; SD, standard deviation.

Because of the similarity between the SDs before adjustment, matching for this variable, in addition to mean age at CS initiation, has very minimal impact on the ITC results, as shown in Table F for age at LOA. Thus, the base-case is still considered an appropriate estimate of the relative treatment effect between givinostat and ECM, with the point estimate for the adjusted HR of 0.190 lying well within the 95% CIs from the alternative analyses.

**Table F: Comparison of findings in the base-case and sensitivity analyses for age at LOA: givinostat vs. ECM (UK real-world data) | Exploring including SD in analyses**

| Treatment arm | Model | N/ESS | Events | Median survival (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|
| Givinostat base-case | Unadjusted | 148 | 43 | 17.97 (15.40, NE) | **0.222 (0.153, 0.323)** |
| Givinostat base-case | Adjusted | 105.1 | 36 | NE (23.32, NE) | **0.190 (0.124, 0.290)** |
| Givinostat base-case with additional adjustment for SD | Adjusted | 108.2 | 36 | 17.97 (15.40, NE) | **0.197 (0.131, 0.297)** |
| Givinostat all patients SA | Unadjusted | 224 | 78 | 17.25 (15.4, NE) | **0.241 (0.176, 0.330)** |
| Givinostat all patients SA | Adjusted | 151.9 | 63 | 17.97 (15.26, NE) | **0.201 (0.142, 0.285)** |
| Givinostat all patients SA with additional adjustment for SD | Adjusted | 155.7 | 63 | 17.97 (15.26, NE) | **0.201 (0.142, 0.285)** |

**Bold** text indicates a significant difference between treatments.
Abbreviations: CI, confidence interval; ECM, established clinical management; ESS, effective sample size; HR, hazard ratio; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NE, not evaluable; OLE, open-label extension; SD, standard deviation.

As the differences between the age at LOA comparisons presented in Table F are minimal, and due to the use of acceleration factors when estimating patient outcomes across age at LOA, NIV and FVC <1L (as described in the CS Section 2.8.2), comparisons for age at NIV and age at FVC <1L experience a similarly minimal impact across the alternative ITCs. Consequently, these results are not presented.

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| 4. Source of data to inform comparative treatment efficacy | Yes (see Appendix Tables 1 and 2) | As outlined in the CS Section B.2.8.1, the comparative efficacy estimates were informed by data from the EPIDYS randomised controlled trial (RCT) and the OLE for givinostat, and by published UK real-world data for ECM (i.e. North Star data from three centres presented by Pietrusz[3,4]).<br><br>In response to EAG feedback requesting greater clarity on the study selection process, Appendix Table provides a topline summary of the rationale for selecting the real-world data sources for the ITC, while Appendix Table outlines the detailed reasons for inclusion or exclusion of each potential source identified through the SLR.<br><br>As described in the response to Key Issue 5, the only head-to-head evidence comparing givinostat with placebo comes from the 18-month EPIDYS trial. While this randomised follow-up period is too short to robustly inform long-term outcomes such as LOA, initiation of NIV, or decline in FVC - which are key components of the economic model - the trial provides valuable evidence of short-term clinical benefit. EPIDYS demonstrated statistically significant improvements in functional endpoints relevant to early disease progression, supporting the potential of givinostat to alter the trajectory of DMD in its earlier stages.<br><br>However, due to the slow, progressive nature of DMD, capturing long-term outcomes in a RCT setting is inherently challenging. Extended follow-up would require many years of observation, during which maintaining a placebo arm may become unethical, and patient retention and treatment crossover become increasingly difficult. Given these constraints, long-term RCTs are not feasible in DMD. In this context, the 18-month randomisation period in EPIDYS is significantly longer than the randomised phases seen in other DMD trials, such as the 12-week randomised phase in the ataluren STRIDE 1 and STRIDE 2 trials,[5,6] and the 24-week randomised phase in the vamorolone VISION-DMD trial.[7]<br><br>While the EPIDYS trial offers high-quality short-term data, using it to inform long-term outcomes would require reliance on surrogate relationships. However, the literature linking early functional outcomes to long-term clinical endpoints in DMD is limited and inconsistent (see response to Key Issue 5). For example, the only study offering a quantitative relationship between a short-term functional outcome (10MWT) and a long-term outcome (LOA) uses a two-year follow-up and stratifies patients categorically ((≤7 seconds vs >7 seconds on 10MWT), rather than modelling a continuous relationship.[8] Moreover, there are few longitudinal datasets that follow patients from early functional decline through to late-stage disease, capturing the | The EAG's response is given in Section 2.2 of the Addendum report.<br><br>**Lack of long-term randomised data**<br><br>The EAG acknowledge the challenges with collecting data on the long-term outcomes in DMD from a randomised trial. However, the challenges involved in the data collection do not mean that the uncertainties about givinostat efficacy on long-term outcomes do not exist. Given these uncertainties, the surrogacy approach suggested by the EAG presents a potential alternative approach, but we also acknowledge that this is also likely to have considerable uncertainties.<br><br>The substantial heterogeneity and issues with generalisability across studies in individuals' DMD progression highlighted by the company is one of the concerns raised by the EAG regarding:<br>• The company's use of an unanchored ITC<br>• The company's use of acceleration factors to predict long-term outcomes from Age at LOA.<br>These two approaches both fail to take appropriate consideration for individual-level factors that may impact disease progression.<br><br>If using an aggregate acceleration factor approach for predicting longer-term outcomes is considered suitable, then using more detailed, patient-level, data for surrogacy from shorter-term (EPIDYS) outcomes may also be considered a potential alternative approach (albeit one that is highly uncertain).<br><br>**Source of evidence to inform ECM**<br><br>With regards to the source of evidence to inform long-term ECM efficacy, the company argue here that the UK registry data more closely aligns with the target (UK) population. The EAG agree that this is the case, and that it should be used to inform the natural history baseline. However, for estimating comparative treatment efficacy by matching to EPIDYS/OLE (the unanchored ITC), this source of evidence is poorly aligned.<br><br>The company highlight the greater temporal alignment with EPIDYS/OLE from using the UK registry data source, given that it is collected more recently, which the EAG do accept as an argument. |

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| | | necessary clinical and biological variables to robustly establish predictive relationships.<br><br>Further complicating the development of surrogates is the substantial heterogeneity in DMD progression across individuals - driven by factors such as mutation type and genetic modifiers - which limits the generalisability of findings and hampers validation across different study populations. As a result, building surrogate-based extrapolations from EPIDYS data would introduce considerable uncertainty. Nevertheless, in response to Key Issue 5, the Company has provided a summary of the available evidence predicting long-term outcomes from EPIDYS endpoints and demonstrates that, despite limitations, the published literature supports the extrapolations used in the ITCs and economic model.<br><br>Given these considerations, the UK real-world dataset represents the most appropriate source of long-term data for ECM in the ITCs. Under Key Issue 4, the EAG highlighted several limitations of this approach:<br>• Due to limited availability of baseline characteristics, matching could only be conducted using age at CS initiation, with no ability to adjust for other key prognostic factors or effect modifiers (EAG report, page 68).<br>• Patients enrolled in clinical trials generally have better prognoses than those in routine clinical practice, introducing potential bias when comparing trial populations with registry data, particularly where differences in inclusion/exclusion criteria exist (EAG report, page 68).<br><br>The EAG expressed a preference for an alternative analysis using the CINRG Duchenne Natural History Study (DNHS) registry, citing the inclusion of two additional matching variables – age at diagnosis and duration of deflazacort use (≥12 months) – as a reason for this preference. While the Company provided this analysis to align with previous methods used in the NICE HST22 appraisal (ataluren), it maintains that the CINRG DNHS dataset is not appropriate to inform the base-case analysis.<br><br>The CINRG DNHS dataset is outdated and is not comparable to the givinostat data sets. The most recent CINRG data were collected nearly a decade ago and the oldest data are approximately 19 years old (data collection: 2006-2016) and do not align temporally with the EPIDYS, OLE, or UK real-world datasets (data collection: June 2017–February 2022, October 2017–December 2023, and March 2007-October 2022, respectively). The CINRG registry is also comprised of largely North American centres, whereas EPIDYS enrolled a substantially higher proportion of participants from the UK and Europe (including UK) (7.3% and 67.0%, respectively). These regional | The geographical region may also align slightly better between EPIDYS/OLE and the UK registry than with CINRG DHNS, though overlap with either ECM data source is likely to be relatively poor with regards to geographical region.<br><br>However, the UK registry study does not report key prognostic factors that it would be critical to balance for the unanchored ITC to be valid, such as age at diagnosis and proportion of patients on deflazacort (among many others). Unlike in the UK registry study, these two prognostic factors *are* reported in CINRG DNHS. Whilst matching on these factors substantially reduces the Effective Sample Size (ESS), *it is because of the ability to match on these additional prognostic factors that the ESS is reduced.*<br><br>The ESS is a statistical indicator of the degree of overlap. However, it is highly related to the number of prognostic factors used in matching. The lesser reduction in ESS when matching to the UK registry study rather than CINRG DHNS is not suggestive of good overlap, but simply that *there is not observed data on those prognostic factors to assess the degree of overlap*.<br><br>The EAG therefore do not believe that matching trial data to *either* of these observational evidence sources is likely to be robust but given the limitations of both, the EAG continue to believe that the CINRG DHNS dataset is likely to more closely match EPIDYS/OLE due to the greater potential to match on observed prognostic factors known to be important. The EAG acknowledge that there are arguments for and against both data sources but also feel the need to highlight the substantial differences in results from using either data source over the other, and the inherent uncertainty from an unbalanced observational comparison. |

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| | | differences affect patient demographics, standards of care, and clinical outcomes, further limiting comparability.<br><br>The lack of comparability between the CINRG DNHS and givinostat datasets is highlighted by the substantial reduction in ESS after matching (ESS=37.2), which indicates poor overlap between the CINRG registry and the givinostat trial population. This small ESS has the potential to make the ITC estimates unstable, such that if it were possible to include additional patients in the analysis, the results could be significantly impacted and as such, the robustness and generalisability of any resulting comparative estimates are compromised.<br><br>The UK real-world data aligns more closely with the givinostat data collected in EPIDYS and the OLE, based on time of data collection and setting. Therefore, this is considered the more robust dataset.<br><br>The Company recognises the importance of aligning the comparator population with the givinostat trial population for the ITC. However, given the limitations of the CINRG DNHS dataset outlined above and the considerably better clinical relevance of the UK real-world dataset compared with the givinostat data, the Company considers the UK real-world dataset to remain the most appropriate source for informing ECM outcomes within the economic model. | |
| 5. Impact of potential bias arising from absence of randomised comparisons for key outcomes at longer-term timepoints | Yes | As outlined in the response to Key Issue 4, the EPIDYS trial provides the only head-to-head randomised evidence comparing givinostat with placebo. This 18-month trial offers robust data on short-term clinical outcomes and demonstrated statistically significant improvements in functional endpoints relevant to early-stage DMD. These results support the potential of givinostat to modify the course of disease progression.<br><br>While the randomised follow-up in EPIDYS does not capture long-term outcomes such as LOA, initiation of NIV, or decline in FVC - which are key drivers in the economic model - this limitation is a broader challenge inherent to the clinical development landscape in DMD. The slow and variable nature of disease progression, combined with ethical and practical constraints, makes it difficult to conduct long-duration placebo-controlled trials in this setting. Extended follow-up would require many years, during which issues such as patient retention, crossover, and the ethical acceptability of a long-term placebo arm become increasingly complex.<br><br>Importantly, the EPIDYS trial includes a substantially longer randomised period than many other DMD studies. For instance, the STRIDE 1 and STRIDE 2 trials of ataluren included only a 12-week | The EAG appreciates the additional information highlighted by the company that supports the relationship between short-term outcomes that were evaluated in the randomised phase of EPIDYS, with the long-term economic model outcomes. The EAG acknowledge that there is a relationship/correlation between these different outcomes, and we do not dispute that the randomised findings in EPIDYS suggest a clinically meaningful effect. However, understanding the *magnitude* of efficacy of givinostat on those outcomes is critical to estimating the cost-effectiveness of givinostat, and this is highly uncertain.<br><br>The company have performed a calculation that explores the relationship between 10MWT and LOA by applying an odds ratio calculated from Mazzone et al. (2013)[8] for the relationship between 10MWT ≤7 seconds and the risk of LOA within 24 months follow-up. Note that in this calculation, the Mazzone OR is only applied to the ECM arm in EPIDYS to demonstrate that this provides a lower risk of LOA in ECM patients than would be predicted by the cost-effectiveness model. However, the same calculation is not applied to givinostat patients in EPIDYS, so it is not possible to directly assess |

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| | | randomised phase,[5,6] while the VISION-DMD trial of vamorolone included a 24-week randomised phase.[7]<br><br>Although EPIDYS offers high-quality evidence on early disease progression, informing long-term outcomes requires extrapolation through surrogate relationships. However, the current literature contains limited and variable evidence linking short-term functional measures to later-stage clinical endpoints in DMD. The disease's heterogeneity, driven by factors such as genotype and individual disease modifiers, further complicates the establishment of generalisable surrogate relationships. As such, building predictive models from EPIDYS data would introduce substantial uncertainty.<br><br>In response to Key Issue 5, evidence is provided to support the observed outcomes from the EPIDYS trial and the predicted outcomes used in the economic model. While some of these publications were included in the original CS, they are now described in the context of the observed outcomes from EPIDYS to support the predictions of the economic model. Additionally, any new studies published since the time of submission have been included.<br><br>**Time to run or walk 10 metres (10MWT)**<br><br>Table G presents the baseline and end of study (EOS) assessments of 10MWT for givinostat and placebo from the EPIDYS study (Table 14.2.7.1.1, CSR).<br><br>**Table G: 10MWT baseline vs. EOS from EPIDYS**<br><br>\| \| Givinostat \| Placebo \| Difference \|<br>\|---\|---\|---\|---\|<br>\| Baseline \| 5.41 \| 5.18 \| -0.23 \|<br>\| EOS \| 6.04 \| 7.99 \| 1.95 \|<br><br>Abbreviations: 10MWT, time to run or walk 10 metres; EOS, end of study.<br><br>Mazzone et al. (2013) report 24-month longitudinal data in ambulant boys with DMD, identifying predictors of LOA over two years.[8] One key finding is that boys with a 10MWT of ≤7 seconds had a significantly higher risk of losing ambulation, with an odds ratio of 7.9 (95% CI: 2.2–28.3; p=0.002), compared with those with a 10MWT >7 seconds.<br><br>Using the EPIDYS EOS (18 months) as a baseline, two years post-EOS corresponds to approximately 3.5 years in the model. At this timepoint, the CEM predicts 94.68% of boys in the givinostat arm remain ambulant. Applying the odds ratio from Mazzone et al. (2013) to the 10MWT distribution in EPIDYS suggests that only 69.2% of boys in the ECM arm would retain ambulation after 3.5 years, compared with 79% predicted by the CEM.[8] This suggests that the model may be | what impacts using the Mazzone OR would have on EPIDYS data in a fair and balanced way.<br><br>If the company were to provide estimates in which they apply the same calculation to the givinostat patients in EPIDYS then this comparison might be more informative. As it currently is implemented, the calculation simply demonstrates that, using the Mazzone OR (for predicting LOA from 10MWT) underpredicts the age at LOA versus the model. It may do that in both arms (which in fact may therefore suggest that the model is overpredicting the age at LOA more generally).<br><br>The company also provides further evidence (from Arora et al. 2018[9] and Duong et al 2021[10]) that 10MWT and 4SC are strongly predictive of LOA. However, if this is the case then it suggests that an alternative approach that uses randomised data from EPIDYS to predict age at LOA may be of additional benefit to inform decision-making.<br><br>By using a non-randomised comparison (unanchored ITC) to inform the long-term outcomes, this potentially introduces significant bias compared to if randomised evidence was available on long-term outcomes. Whilst the EAG acknowledge that the challenges in collecting randomised efficacy data on long-term outcomes are inherent to the disease area, and that using short-term randomised outcomes to predict long-term outcomes may also introduce uncertainty, this does not resolve the potential bias that arises from the use of a non-randomised comparison that is likely to be unbalanced in prognostic factors.<br><br>The EAG's response is given in Section 2.3 of the Addendum report. |

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| | | overestimating ambulation rates in the ECM arm and, consequently, underestimating the relative treatment effect of givinostat.<br><br>These data support the predicted relative treatment effect between givinostat and ECM and suggest that the modelled treatment difference may be conservative.<br><br>While Arora et al. (2018)[9] and Duong et al. (2021)[10] do not provide a direct quantitative relationship, both studies offer supportive evidence that the differences observed in the 10MWT between the givinostat and placebo arms at the EOS in EPIDYS are clinically meaningful:<br><br>• Arora et al. (2018) present longitudinal data from the ImagingDMD natural history cohort, evaluating timed function tests (TFTs), including 10MWT and 4SC, in boys with DMD.[9] The study reports a high predictive value of 10MWT for subsequent LOA, with an area under the ROC curve (AUC) of 0.93 (95% CI: 0.88–0.97), indicating strong ability of the 10MWT in predicting LOA within one year.<br>• Duong et al. (2021) assess the minimum detectable change (MDC) and minimal clinically important difference (MCID) in the annual rate of change in TFTs, including 10MWT and 4SC.[10] The study reports statistically significant MDC and MCID values of –0.138 m/sec and –0.212 m/sec, respectively. These results suggest that the observed difference in EPIDYS (mean change of 1.95 seconds) exceeds the threshold for both a real and clinically meaningful change in ambulatory function.<br><br>Additional evidence from McDonald et al. (2013, 2024)[11,12] and Bushby et al. (2011)[13] further support the clinical relevance of 10MWT thresholds, showing that times exceeding 10 or 12 seconds are associated with an increased risk of LOA. Although patients in the EPIDYS placebo arm had not yet reached these thresholds at EOS, the trajectory of decline indicated they were likely to do so sooner than those patients in the givinostat arm.<br><br>Finally, Humbertclaude et al. (2012) report on a strong correlation between loss of ability to run and age at LOA with an r value of 0.85, p-value <0.0001.[14]<br><br>**Time to climb 4 stairs (4SC)**<br><br>Table H presents the baseline and EOS assessments of 4SC for givinostat and placebo from the EPIDYS study (Table 20, CSR). | |

**Table H: 4SC baseline vs. EOS from EPIDYS**

| | Givinostat | Placebo | Difference |
|---|---|---|---|
| Baseline | 3.39 | 3.48 | 0.09 |
| EOS | 4.70 | 6.37 | 1.67 |

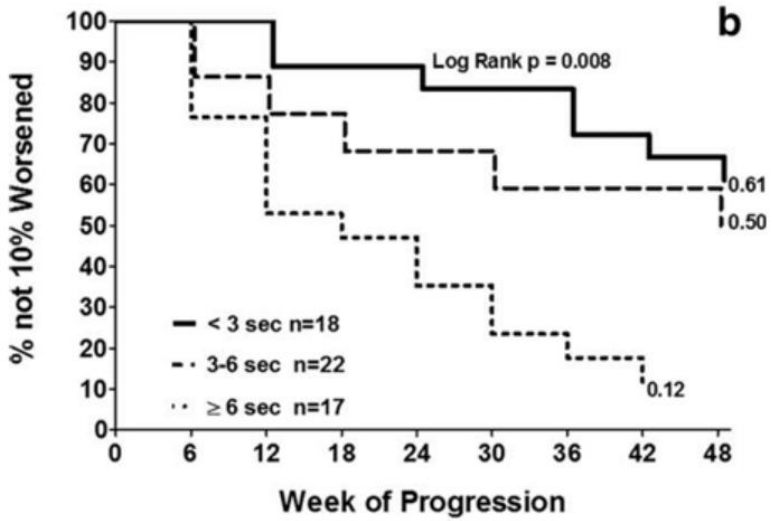
Abbreviations: 4SC, time to climb 4 stairs; EOS, end of study.

While no data were identified providing a direct quantitative relationship, Arora et al. (2018) and Duong et al. (2021) offer supportive evidence that the differences observed in the 4SC between the givinostat and placebo arms at the EOS in EPIDYS are clinically meaningful:

- Arora et al. (2018) report a high predictive value of 4SC for subsequent LOA, with an AUC of 0.96 (95% CI: 0.92–0.99), indicating strong ability of the 4SC in predicting LOA within one year[9]
- Duong et al. (2021) report statistically significant MDC and MCID values of –0.034 task/sec and –0.035 task/sec, respectively.[10] These results suggest that the observed difference in EPIDYS (mean change of 1.67 seconds) exceeds the threshold for both a real and clinically meaningful change in ambulatory function.

Additional evidence from McDonald et al. (2013) further supports the clinical relevance of 4SC endpoints, showing that times <3 seconds, 3–6 seconds, and ≥6 seconds are associated with an increased risk of 10% worsening of disease progression (Figure D).[11]

**Figure D: Relationship between 4SC and % not 10% worsened | McDonald et al. (2013)[11]**




Abbreviations: 4SC, time to climb 4 stairs; sec, seconds.

Finally, Humbertclaude et al. (2012) report on a strong correlation between loss of ability to climb stairs and age at LOA with an r value of 0.84, p-value <0.0001.[14]

**Time to rise from floor (TTR)**

Table I presents the baseline and EOS assessments of TTR for givinostat and placebo from the EPIDYS study (Table 14.2.2.1.1, CSR).

**Table I: TTR baseline vs. EOS from EPIDYS**

| | Givinostat | Placebo | Difference |
|---|---|---|---|
| Baseline | 5.57 | 5.59 | 0.02 |
| EOS | 14.43 | 19.17 | 4.74 |

Abbreviations: EOS, end of study; TTR, time to rise from floor.

While no data were identified providing a direct quantitative relationship, Duong et al. (2021) offer supportive evidence that the differences observed in the TTR between the givinostat and placebo arms at the EOS in EPIDYS are clinically meaningful:

- Duong et al. (2021) report statistically significant MDC and MCID values of –0.026 rise/sec and –0.023 rise/sec, respectively.[10] These results suggest that the observed difference in EPIDYS (mean change of 4.74 seconds) exceeds the threshold for both a real and clinically meaningful change in ambulatory function.

Additional evidence from McDonald et al. (2022)[15] and Zambon et al. (2022)[16] indicate differences in LOA based on TTR. However, the cut-offs they use do not align with the EOS data from EPIDYS. Zambon et al. (2022) show that TTR at baseline was positively associated with age at LOA with a hazard ratio of 1.13 (95% CI: 1.09–1.17).

Finally, Humbertclaude et al. (2012) report on a strong correlation between loss of ability to rise from the floor and age at LOA with an r value of 0.91, p-value <0.0001.[14]

**Weight and height**

Table J and Table K present the baseline and EOS assessments of weight (kg) and height (cm) for givinostat and placebo from the EPIDYS study (Table 70, CSR).

**Table J: Weight (kg) baseline vs. EOS from EPIDYS**

| | Givinostat | Placebo |
|---|---|---|
| Baseline | 31.22 | 32.58 |
| EOS | 33.96 | 37.49 |
| Change from baseline | 2.97 | 4.68 |

Abbreviations: EOS, end of study.

**Table K: Height (cm) baseline vs. EOS from EPIDYS**

| | Givinostat | Placebo |
|---|---|---|
| Baseline | 125.1 | 126.7 |
| EOS | 129 | 131.3 |
| Change from baseline | 3.8 | 4.3 |

Abbreviations: EOS, end of study.

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| | | Stimpson et al. (2024) analysed data from 648 boys with DMD treated with glucocorticoids, using 2,228 observations from the UK NorthStar database collected between 2006 and 2020.[17] The research aimed to understand how growth patterns influenced the risk of losing ambulation.<br><br>The authors found that the cumulative hazard of LOA was significantly increased by yearly weight standard deviation (SD) gain. That is, a child with a yearly weight gain 0.25SD greater than an average child has a 90% (95% CI 33%–171%) greater risk of LOA. Additionally, reduced height gain, significantly decreased the risk of LOA. Notably, a yearly height stunting of 0.25SD relative to the average height-for-age increase in the non-DMD population was associated with a 74% (95% CI 14%–167%) reduction in risk of LOA.[17] However, it was unclear over what period these reductions in risk were relevant to.<br><br>In terms of SDs from EPIDYS, the placebo arm had a weight gain of 1.21SD, while givinostat had a weight gain of 0.82SD. The difference in SDs is 0.39SD. Therefore, this meets the 0.25SD threshold. The placebo arm had a height change of 1.37SD, while givinostat had a height change of 1.18SD. The difference in SDs is 0.19SD. Whilst these data do not yet meet the threshold, the data are trending as supportive for givinostat.<br><br>Earlier data presented by Stimpson et al. (2022) supported a relationship between growth patterns and LOA.[18] However, the relationship was less pronounced, for ambulant boys between the ages of 10 and 11 for every 0.25SD taller the patient was there was an associated 6% increase in the risk of losing ambulation during follow up.<br><br>**Conclusions**<br><br>Although RCTs are typically considered the gold standard for estimating treatment efficacy, long-term outcomes in DMD are difficult to capture due to the disease's slow progression. The 18-month EPIDYS trial provides valuable randomised evidence on short-term functional outcomes and is longer than comparable studies in DMD. However, using these data to inform long-term outcomes like LOA or respiratory decline requires surrogate relationships, which remain limited and variable in the literature.<br><br>Only one study, Mazzone et al. (2013), provides sufficient data to estimate the probability of LOA based on 10MWT; however, this analysis is limited to a two-year follow-up and applies a threshold that may not be sensitive enough to support long-term extrapolation.[8] The | |

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| | | published studies do confirm that the outcomes observed in EPIDYS are clinically meaningful.<br><br>Due to insufficient data to robustly model surrogate relationships from the EPIDYS study, the model adopts a more robust approach using the UK real-world data[2,3] as the external control arm. This approach is aligned with that taken in the ataluren NICE submission[19]. An additional advantage of this approach is that it allows for the use of the Project HERCULES CEM which is driven by endpoints extensively validated by clinicians and patient representatives and aligns with the model structure accepted by NICE in the vamorolone appraisal in DMD (NICE TA1031).[20]<br><br>As discussed in response to Key Issue 4, this approach is further justified by the comparability of the UK real-world data to the givinostat dataset and the consistencies observed in the literature between placebo arms of clinical trials and UK real-world data in DMD.<br><br>Therefore, while the EPIDYS RCT provides strong short-term efficacy signals, its limited follow-up precludes its use for long-term modelling. The use of long-term givinostat data combined with a UK real-world external control arm offers a more reliable and evidence-based approach to estimating long-term comparative effectiveness. | |
| 6. Use of 1.5% discounting | Yes | The EAG presents an inconsistent description of the application of the 1.5% discount rate (e.g. page 13 of the EAR) which may be interpreted as the Company applying a 1.5% discount rate to health outcomes across the model time horizon. To clarify, in the base case, the 1.5% discount rate has been applied from year 30 onwards, in accordance with guidance from the HM Treasury Green Book.<br><br>The justification for using the 1.5% discount rate has been discussed in detail in Section B.3.2.2 of the CS and in the response to CQ B23. Rather than repeating those points, we provide further evidence supporting the appropriateness of applying the 1.5% discount rate beyond 30 years. We also note that this approach may be conservative and that applying a 1.5% discount rate across the full time horizon for health outcomes could be more relevant in the context of givinostat.<br><br>The EAG raises several concerns, including that applying the 1.5% rate beyond 30 years deviates from NICE's reference case; that previous DMD appraisals (e.g. vamorolone and ataluren) used a 3.5% rate across the full time horizon; that existing published DMD models also adopt the 3.5% rate; and that there is currently no long-term evidence of benefit for givinostat from RCTs or cohort studies. They also highlight that the long-term benefit of givinostat, particularly post-discontinuation, remains uncertain. | In Key Issue 6 of the EAR the EAG clearly state *"The company uses a 1.5% discount rate for benefits beyond 30 years (and argues for a 1.5% discount rate for benefits for the whole time horizon)."* The EAG view is that this accurately characterises the company's base case.<br><br>The NICE methods guide specifies that non-reference-case discounting can be applied only if the following three conditions are met:<br><br>1. The technology is for people who would otherwise die or have a very severely impaired life.<br><br>2. It is likely to restore them to full or near-full health.<br><br>3. The benefits are likely to be sustained over a very long period.<br><br>The EAG accepts that DMD severely impacts quality of life and thus meets the first criterion. However, the company has not provided any evidence for the second criteria, and the EAG views that provided for the third to be limited. The randomised period of EPIDYS was only 18 months and the OLE only 1204.2 days (i.e., about 3.3 years) while the model time horizon is lifetime for patients initially aged 6 years old, and the company is arguing for 1.5% discounting after 30 years. |

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| | | As detailed in our response to CQ B23, givinostat meets two of the three criteria for applying non-reference discounting, as outlined in the NICE Methods Manual.[21] Specifically, it is indicated for a condition that severely impairs quality of life, and is expected to deliver sustained benefits. These criteria support the assumption of a 1.5% discount rate for health outcomes beyond 30 years and provide support that the 1.5% discount rate may be appropriate across the model time horizon.<br><br>NICE has accepted non-reference discounting in prior evaluations where long-term benefit and disease severity justified deviation from the standard 3.5% rate:<br><br>1. **Onasemnogene abeparvovec (Zolgensma®) for SMA (HST15, 2021)**[22]<br>NICE accepted a 1.5% discount rate for health outcomes, acknowledging the life-threatening nature of SMA and the potential for long-term benefit, despite uncertainties in durability.<br>2. **Strimvelis® for ADA-SCID (HST7, 2018)**[23]<br>The 1.5% rate was accepted due to the potential for sustained benefit. While the committee acknowledged some uncertainty around whether the criteria were fully met, it concluded that both discount rates should be considered during decision-making.<br>3. **Dinutuximab beta for high-risk neuroblastoma (TA538, 2018)**[24]<br>NICE accepted the 1.5% discount rate, based on the potential for cure in a subset of patients for both costs and outcomes.<br><br>As noted in our response to CQ B23, vamorolone met only one of the non-reference discounting criteria, and ataluren was routed through the HST process under a previous version of the NICE Manual, when non-reference discounting criteria had not yet been formally introduced. Thus, comparisons to these appraisals are not directly applicable.<br><br>The EAG references published models in DMD using a 3.5% discount rate, yet it also acknowledges that these are hypothetical models. These models were not designed to assess non-reference discounting under current NICE guidance, and should not be interpreted as precedent that precludes a 1.5% discount rate in the case of givinostat.<br><br>While it is true that no RCT or cohort study extends over the full duration of expected benefits for givinostat, it is incorrect to conclude that there is no evidence of long-term benefit.<br><br>As outlined in the CS, we have robust evidence from both the 18-month randomised EPIDYS trial and its OLE, together comprising one of the longest clinical follow-up periods for any investigational therapy in DMD. This randomised period is longer than the studies | The EAG therefore maintains that non-reference-case discounting is not justified and the base case discounting should remain 3.5%. |

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| | | underpinning both the ataluren and vamorolone NICE submissions.[19,20] The mean duration of follow-up from the OLE was 1,204.2 days (SD ±446.3; median 1,179.0 [range 99 to 2,259] days). Importantly, givinostat has demonstrated consistent benefit across early TFT endpoints in EPIDYS, and these benefits are shown to translate into long-term outcomes in the OLE. Feedback from UK clinical experts highlights that the delay in LOA observed for givinostat in the OLE, will then have an impact on the overall progression of the disease in the non-ambulatory health states.<br><br>It is also important to acknowledge the realities of trial design in DMD. Clinically meaningful long-term outcomes, e.g. LOA, may not occur until many years after treatment initiation. In UK clinical practice, the typical time from age six (the approved starting age for givinostat per the SmPC) to LOA is approximately six years. Conducting a placebo-controlled RCT over such a period would be unethical and infeasible. These challenges become more relevant when exploring outcomes beyond LOA.<br><br>In addition to the evidence already provided, it is important to recognise that treatment for boys with DMD typically begins at an early stage. However, the most meaningful clinical and patient outcomes take several years or even decades to fully materialise. While the EPIDYS trial demonstrates the clinical benefits of givinostat, the outcomes that are most significant to patients, and which drive costs in the economic model, become apparent over the patient's lifetime. Consequently, the full value of givinostat becomes apparent only many years after treatment initiation.<br><br>**Despite this delay, these long-term outcomes are important to both patients and caregivers today. Therefore, we believe that, in addition to meeting two of the three criteria for non-reference discounting, the 1.5% discount rate is contextually appropriate for givinostat. This rate accurately reflects the long-term nature of the therapy's benefits, while ensuring that its value is appropriately recognised.** | |
| 7. Overestimation of caregiver utility impact | Yes – BOI report | As discussed during our factual accuracy check and the TE call on 2nd April 2025, one of our key concerns is that our approach to modelling caregiver QALYs has only been partially explained in the EAR. This partial explanation raises the risk of misinterpretation, particularly when comparing our methodology with that of the EAG. During the TE call, the EAG acknowledged that, due to time constraints, they were unable to fully describe the Company's base case approach to modelling caregiver QALYs, instead focusing on detailing their own approach. Unfortunately, this is not made clear in the EAR, and as a result, there | Thank you for re-stating company's preferred assumptions / methods. The EAG's preferred assumptions/methods along with the evaluation of company's methods are provided here. This section refers to the Landfeldt study, for which the reference is given at the end of the section.<br><br>The caregiver utility issue is influenced by a number factors within the economic model: i) the source of the utility values used, ii) the methods for calculating the utility increments / decrements, iii) the |

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| | | is a risk that a reader may draw incorrect conclusions from the way the Company's approach is presented.<br><br>For example, Table 28 of the EAR states that the utility decrements shown reflect burden of illness (BOI) values used in the Company's economic model. This is incorrect – the values presented are not BOI figures but are instead utility decrements derived from the UK vignette time trade off (TTO) study. In addition, the EAR (page 95) states that the Company applies a bereavement disutility. This statement is misleading. A bereavement disutility is typically applied in each model cycle to the proportion of patients who have died, across the entire time horizon. However, as outlined in Section B.3.4.6 of the CS and in response to CQ B14, we have applied a utility decrement to the incremental time spent in the death health state. Since givinostat reduces time spent in this state, it results in negative incremental time in the death state. When this is multiplied by the utility decrement, it yields a positive utility gain for caregivers. This is more accurately described as a utility benefit from extended survival with givinostat, rather than a bereavement disutility, and should not be misrepresented as such.<br><br>In our response, we have structured the discussion around three key areas: methodology, data sources, and the number of caregivers. The only new evidence submitted at this stage is the BOI report from Project HERCULES, which has been shared with NICE and clarifies the source of caregiver HRQoL data used in both the vamorolone NICE submission and the EAG's base case.[20,25] This is addressed in the relevant section below. While no further additional evidence is provided, we have included a comparison of the Company's base case and the EAG's approach within each section to help prevent any potential misinterpretation.<br><br>**Methodology**<br><br>Table L compares the methodological approaches in the Company's base case and the EAG's base case. | methods for accruing Quality of life for carers, iv) the number of caregivers, and v) the application of the utility values in the death state.<br><br>i) The caregiver utility values used in the company economic model are presented in Addendum Table 4. As discussed in section 4.2.7 of the EAG main report there is insufficient evidence to support use of the vignette study and the EAG point to alternatives such as the BOI study values supplemented with the Landfeldt values for health states 5, 6 and 7, as in TA301. The EAG model the caregiver utility values on the EQ-5D-3L, reported by Landfeldt et al.as presented in Table 4 in the EAG report Addendum).<br><br>ii) The EAG's method is to calculate the caregiver utility decrements relative to the utility values for carers in the least severe state is a common method in appraisals of this disease area and was selected by the committee in TA1031. The company's caregiver utility decrements / increments are calculated relative to healthy individuals in the general population (0.923) and are therefore substantially larger than the EAG's base case. The EAG's base case uses the utility decrements from the Landfeldt study as reproduced in Table 5 in the EAG report addendum.<br><br>iii) The company's preferred method for accruing the carer quality of life is relative to midway health state. This involves rescaling the utility decrements in **Error! Reference source not found.** to increments/ decrements in **Error! Reference source not found.**. The rescaled values are then applied to the incremental life years (Givinostat minus ECM) in each cycle of the model. The EAG finds the choice of midway health state to be subjective and not backed by evidence. The method is novel, but the EAG prefer the more commonly applied disutilities method to modelling the carer quality of life. Details of this issue, with a comparison of both methods, are presented in section 4.2.7 of the main EAG report.<br><br>iv) The company assumes that the number of caregivers is constant at 2, but the EAG prefers to model the increasing burden of care by modelling 1 caregiver for health states 1-3, increasing to 2 caregivers for health states 4-8. |

**Table L: A comparison of methodological approaches to modelling caregiver QALYs**

| | Company base case approach | EAG approach |
|---|---|---|
| **Approach** | Increments relative to midway health state | Disutility |
| **Summary** | Utility increments or decrements are applied to the incremental patient LYs across all health states (including the death health state). This gives the incremental caregiver QALYs. | Utility decrements are applied to the total patient LYs across living patient health states in the givinostat and ECM arms. The incremental caregiver QALYs are then calculated by the difference between the givinostat and ECM arms. |
| **Justification** | The approach reflects the impact of givinostat on caregiver QALYs:<br>• Extended duration in the milder health states are reflected by additional caregiver QALYs.<br>• Extended duration in the more severe health states are reflected by less caregiver QALYs.<br>• Modest impacts across the patient health states. The extended duration for which the patient is alive | The approach:<br>• Page 20, EAR: "anchors at the early ambulatory health state and represents progressively worsening quality of life in subsequent health states."<br>• Page 20, EAR: "has the added benefit of being directly compatible with utility values used in other appraisals of DMD"<br>• Page 95, EAR: "quality of life is accounted for on both ECM and givinostat arms, as otherwise an imbalance is created"<br>• Page 95, EAR: Does "not include the utility decrement for dead patients, otherwise referred to as the |

v) The company assumes that there is a utility benefit from extended survival due to treatment with givinostat, this is achieved by combining the method of modelling caregiver QoL relative to the mid-way health state along with the assumption of two caregivers in health state 9 (the death state).

The EAG notes a survival benefit of treating patients with DMD could be modelled as a treatment effect, taking into account available clinical evidence on the difference in survival between givinostat and ECM groups. Such evidence was not made available and therefore we consider the survival benefit to be unsubstantiated.

In the CS, the company refer to ongoing research on modelling caregiver QoL, (CS, Doc B. References 231 to 235) but NICE methods for this have not been prescribed. The CS also references a review of NICE submissions for disease-modifying therapies (DMTs) for multiple sclerosis, Alzheimer's disease, and spinal muscular atrophy notes carers' QoL modelled by attaching a carer utility or disutility to the patient's health state. (Pennington, 2024)

The EAG prefers using the disutility approach to modelling caregiver QoL combined with assigning with zero carers in health state 9 and ascribing a bereavement disutility with the value of zero.

Additional references:

Landfeldt E. Measuring health-related quality of life in Duchenne muscular dystrophy: Current perspectives and recommendations. Journal of the neurological sciences 2023;446120545

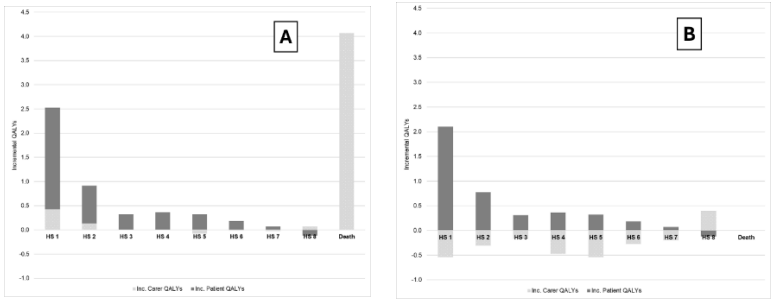
Pennington, B., Al-Janabi, H. Modelling Informal Carers' Health-Related Quality of Life: Challenges for Economic Evaluation. *Appl Health Econ Health Policy.* 2024. **22**, 9–16

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| | is reflected by additional QALYs. | bereavement disutility” |
| **EAG critique** | • The method results in a faster rate of carers’ QALYs accruing over shorter periods of time in comparison to the disutility method.<br>• Imbalance created from only considering caregiver QALYs based on incremental patient LYs.<br>• Insufficient evidence for the “bereavement disutility” | NA |
| **Company critique** | NA | The approach has no face validity. Givinostat is shown to accrue fewer caregiver QALYs across all living health states, except for health state 8 (the most severe health state) for which there is shown to be a benefit to the caregiver. This results in an overall caregiver detriment applied to givinostat. |

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, Evidence Assessment Group; EAR, Evidence Assessment Report; ECM, established clinical management; NA, not applicable; QALY, quality adjusted life year.

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| | | Figure E illustrates the comparison of incremental (discounted) patient QALYs and caregiver QALYs derived from the Company's and EAG's base case approaches. Please note that utility decrements associated with AEs and spinal fusion surgery are excluded from the patient QALYs presented in these diagrams. To ensure a fair methodological comparison, both approaches assume the same utility source (the UK TTO vignetter study) and a single caregiver.<br><br>In the Company's approach, modest caregiver QALY gains are observed alongside increases in patient QALYs in health states 1 to 3 (with gains in health state 3 being negligible). No change in caregiver QALYs is seen in health state 4, as it serves as the anchor state. For health states 5 to 7, slight losses in caregiver QALYs accompany the increased patient QALYs, while a small gain in caregiver QALYs is observed in health state 8 due to reduced time spent in this state. The primary driver of caregiver QALY gains is the improvement in patient survival associated with givinostat, which is captured as a positive QALY benefit from reduced time spent in the death health state.<br><br>In contrast, the EAG's approach shows caregiver QALY losses for all health states where patient QALYs increase, and a corresponding gain in health state 8 when patient QALYs decrease. Notably, the EAG's method does not directly capture the impact of improved survival with givinostat, although there is an indirect effect through changes in time spent across health states.<br><br>As discussed in Table L, we believe the Company's approach better reflects the real-world experience of caregivers over time, aligning with face validity – particularly in recognising the positive impact on caregivers from extended patient survival (i.e. time avoided in the death health state). In contrast, we find it lacks face validity to suggest that improved patient outcomes with givinostat would result in decreased caregiver QALYs. For this reason, our base case continues to assume caregiver utility increments relative to the midpoint health state. | |

**Figure E: Comparison of the incremental (discounted) QALYs accrued by patients and caregivers across the Company's base case (A) and the EAG's base case (B)**




Abbreviations: EAG, Evidence Assessment Group; QALY, quality adjusted life year.

**Data source**

Table M provides a comparison of the data sources used in the Company's base case and the EAG's base case. As outlined in Table M, there has been some confusion and misrepresentation regarding the utility values reported in TA1031 which inform the EAG's base case. Although these values were reported by caregivers, they were intended as proxy assessments of patient HRQoL – not direct measures of caregiver HRQoL. The full BOI report, which provides more detail on these data, has been shared with NICE and the EAG following the TE call to support clarification.

While caregiver HRQoL was assessed in the BOI study using the CarerQoL instrument, it did not generate utility values. As a result, the use of these data as utility inputs reflecting caregiver HRQoL is not appropriate. Therefore, our base case continues to use the utility values derived from the UK caregiver vignette study. As detailed in Section B.3.4.3 of the CS, this is a well-conducted study with 200 respondents, the values have face validity across the health states, and the health states align with the economic model.

**Table M: A comparison of data sources informing caregiver utilities**

| | Company base case approach | EAG approach |
|---|---|---|
| **Source** | UK vignette TTO study | BOI study from TA1031. Note in the TE call, it was highlighted that these values are inappropriate – as discussed below. |
| **Justification** | The data source:<br>• Well-conducted and robust study with N=200 respondents<br>• Aligns with the health states in the model<br>• Face validity of worsening utilities across progression of health states<br>• TTO methodology may be more sensitive to the challenges faced by caregivers of people with DMD | • Page 20, EAR: "The EAG prefer utility decrements relative to the early ambulatory health state from the BOI study, which were also preferred in TA1031, the appraisal for vamorolone" |
| **EAG critique** | • Not comparable with previous NICE appraisals.<br>• The EAG notes while any vignette study maybe accepted as a source of utilities, the NICE methods guide stipulates evidence should be derived from a | NA |

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| | synthesis of peer-reviewed literature to make the case for the inappropriate use of EQ-5D | |
| **Company critique** | NA | As discussed during the TE call, there has been some confusion regarding the BOI values referenced from TA1031. The utility values presented in TA1031 were reported by caregivers but were intended as proxy assessments of patient HRQoL, not as direct measures of caregiver HRQoL. The full BOI report has since been provided to NICE and the EAG following the TE call.<br>While caregiver HRQoL was assessed in the study using the CarerQoL instrument, no utility data were derived from this measure. As such, these values are not appropriate for use in modelling caregiver utilities |

Abbreviations: BOI, burden of illness; EAG, Evidence Assessment Group; EAR, Evidence Assessment Report; ECM, established clinical management; HRQoL, health-related quality of life; NA, not applicable; QALY, quality adjusted life year; TE, technical engagement; TTO, time trade off.

**Number of caregivers**

Table N compares the Company approach to number of caregivers with the EAG's approach. Based on clinical expert feedback received during the committee meetings of the vamorolone NICE appraisal, it was emphasised how the impact of diagnosis and progression of DMD impacts the whole family network (e.g. siblings and grandparents) as well as requiring additional support from outside this network (e.g. schools). Therefore, we consider that the base case of two caregivers is conservative.

**Table N: A comparison of number of caregivers assumed in the caregiver QALYs calculations**

| | Company base case approach | EAG approach |
|---|---|---|
| **Number of caregivers** | Average of two across all health states | One caregiver in ambulatory health states, increasing to two for non-ambulatory health states |
| **Justification** | • Aligning with feedback from clinical experts in the vamorolone NICE submission | • Page 96, EAR: "The EAG prefers modelling an increasing caregiver burden as in the vamorolone appraisal in TA1031, the number of carers on the were assumed to be 1 for ambulatory health states (1-3), and 2 caregivers for non-ambulatory health states" |
| **EAG critique** | Not comparable with previous NICE appraisals | NA |

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| | | **Company critique** | NA | The assumption of two caregivers may be conservative as feedback from patient advocacy groups heard during the second committee meeting for vamorolone emphasised how the impact of diagnosis and progression of DMD impacts the whole family network (e.g. siblings and grandparents) as well as requiring additional support from outside this network (e.g. schools) |
| | | Abbreviations: DMD, Duchenne muscular dystrophy; EAG, Evidence Assessment Group; EAR, Evidence Assessment Report; ECM, established clinical management; NA, not applicable; QALY, quality adjusted life year. | | |
| 8. Costs and quality of life assumed the same in the full ventilation states and night ventilation states | No | The Company acknowledged the limitations of the data informing base case costs and utilities for the full and night-time ventilation health states, as detailed in CQ B17. In response, an alternative scenario analysis was presented to explore this uncertainty. This was limited to a scenario analysis to avoid additional uncertainty from incorporating data from multiple sources within the base case. Additionally, cost estimates from Morgan et al. (2024) represent an average across both night-time and full ventilation health states.[26] Therefore, applying a multiplier to these estimates leads to an overestimation of total costs for patients with DMD.<br>As noted in the EAR (page 22), the EAG preferred using costs and utilities from the BOI study in the base case. This preference is based on the alignment between the BOI health state definitions and those used in the Company's model, including separate estimates for health states 7 and 8.<br>In the EAG's base case, costs were sourced from the vamorolone NICE submission, which references the BOI study and applies a 0.57 multiplier. However, the derivation of this multiplier is unclear, and we | Thank you for your comments<br>The EAG would have preferred to incorporate patient utilities from the clinical trial, but this was not possible for reasons stated by the company in their response to clarification questions B10 and B11. The company's preferred observational study by Audhya et al 2023[27] was not deemed suitable because it reported values on the EQ-5D-5L scale belonging to a set of US patients and valued the US value set. The EAG's discussion of the BOI study is presented in the EAG report section 4.2.7. The EAG therefore continues to use utilities from the BOI study in its base case while agreeing with the company's reservations on the sample size. This was informed by a Delphi panel measured quality of life for patients and caregivers in the UK using EQ-5D as part of Project HERCULES and state definitions align with those of the company model, including separate estimates for states 7 and 8.<br>The EAG's review of the evidence found direct medical costs were well documented in the observational studies but not the cost of medical aids expected to be needed by patients in the higher severity |

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| | | do not have access to the calculations used in the vamorolone NICE submission to assess their validity. Concerns remain regarding the robustness of the BOI study as a data source for the base case. As detailed in Section B.3.5.1 of the CS, BOI cost estimates are based on physician- and patient-reported data from a small number of respondents per health state (ranging from 2 to 15), resulting in large standard errors. While these estimates are aligned with health state definitions, the data are highly uncertain.<br><br>In contrast, the Morgan et al. (2024) cost data (used in the Company's base case) are derived from much larger patient samples: 387 in the ambulatory state, 188 in the non-ambulatory non-ventilated state, and 64 in the non-ambulatory ventilated state.[26]<br><br>Similarly, in the EAG's base case, utility values were also taken from the BOI study. These data are limited, with 0 to 8 responses per health state. In cases where no data were available, utility values defaulted to those from Landfeldt et al. (2017), introducing additional uncertainty through reliance on multiple sources. Furthermore, the BOI utility values are based on the DMDQoL, which is not aligned with NICE's preferred measure, the EQ-5D. In contrast, utility data used in the Company's preferred base case were sourced from Audhya et al. (2023), which used EQ-5D and included response counts ranging from 8 to 23 across health states.[27]<br><br>In response to Key Issue 7, the full BOI report has been shared with NICE and the EAG to provide greater transparency regarding these limitations.<br><br>**Despite the different approaches used to address data limitations, both the Company's and EAG's scenario analyses result in lower ICERs than the base case. Notably, the EAG's scenario results in a greater reduction in the ICER than the Company's. This suggests that the base case ICER may be conservative.** | health states. A comparison of the costing studies and the multipliers calculated for the company's analyses are presented in Table 31 of EAG report (Section 4.2.8).<br><br>The Morgan study[26] has a larger sample and utilises the CPRD database, which is more representative of the UK population, in comparison to the BOI study. Although the health states in the BOI study align well with the natural history model chosen, the EAG agree that the costs in the Morgan study are suitable for decision making despite having been categorised for a fewer number of health states.<br><br>The EAG highlighted that costs for medical aids required by disabled patients at the higher and more severe health states were not included in the company's model. While the EAG appreciates the company's attempt to quantify the costs of medical aids by using a multiplier, there was concern that the multiplier was calculated using indirect medical costs that would not be relevant for decision making in the UK. The EAG accept the company's criticism that the EAG report did not clearly explain the use of an alternative multiplier applied to the BOI study. This is not used in the revised base case (see Addendum report). The costs used in the model are reported in Table 7, in the EAG addendum report. |
| 9. Overestimation by NHM of survival and DMD clinical progression events | No | In Key Issue 9, the EAG highlights that the updated NHM underestimates survival compared to clinical opinion at ages 15, 20, 25, 30, and 35, with alignment only observed at ages 40 and 50 (as shown in Table 24 of the EAR, replicated from Tables 45 and 46 of the CS).<br><br>While it is correct that the updated NHM predicts lower survival than clinical opinion for ages 15–35, the survival estimates remain within the range observed across all available data sources. It is also important to note that the clinical feedback was based on input from six clinicians, which introduces some degree of uncertainty. Therefore, we consider that the survival projections from the updated NHM are consistent with the available evidence. | As explained in Key Issue 8, the EAG identifies that this issue was due to the company's updated NHM only being calibrated, using SOLVER, to 50-year survival estimated by clinical experts (2.8%) and median age at loss of ambulation (12.1 years, as reported by UK real world data).<br><br>The EAG holds that it is inconsistent for the company to maintain that the 50-year estimate, by six clinicians, is a suitable target for calibration and simultaneously discount the underestimation at ages 15, 20, 25, 30 and 35.<br><br>Furthermore, the underestimation was also present when comparing clinical progression to real world data. As noted in Key Issue 8, the model consistently underestimates the age for DMD patients of |

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| | | The EAG has suggested that further cohort studies reporting both survival and DMD milestones would help to resolve this issue. We agree with this recommendation. However, in the absence of such data, we believe the NHM provides a reasonable and evidence-aligned prediction of survival, supported by both existing data and clinical expert opinion. | starting ventilation, starting full time ventilation and death compared to UK real world data (EAG report, Table 25). The EAG therefore maintains that the consistent underestimation of natural history is an issue and likely overestimates the benefit of givinostat as the true natural survival and time to clinical progression (and thus potential for benefit) is greater. |
| 10. Mismatch of HERCULES NHM and available RCT data on givinostat | No | In Key Issue 10, the EAG raised concerns about the model structure used in the Company's base case relative to the randomised evidence from the EPIDYS clinical trial for givinostat. While the EAG acknowledges that the Project HERCULES model, which forms the basis of the Company's base case, provides a strong conceptual framework for DMD, they suggest that integrating the available data from the EPIDYS trial into the Project HERCULES model would be an improvement. The EAG also notes that the Project HERCULES model structure has been accepted in previous appraisals.<br><br>In response to Key Issue 5, we have highlighted that while the EPIDYS trial offers strong signals for short-term efficacy, its limited follow-up restricts its utility for long-term modelling. Therefore, the model instead takes a more robust approach by using UK real-world data as the external control arm. This aligns with the approach taken in the ataluren NICE appraisal.[19] The combination of long-term givinostat data with a UK real-world external control arm provides a more reliable and evidence-based approach for estimating long-term comparative effectiveness. | The EAG reiterate that the HERCULES model structure transition probabilities cannot be directly informed by the primary outcome of EPIDYS (i.e., mean change in the time taken to complete a standard four-stair climb between baseline and 18 months). This leads to the model relying on non-randomised evidence to inform treatment effects, via an uITC, which the EAG has rated as being at critical risk of bias. |

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| 11. Implementation of treatment effect within the economic model | No | As outlined by the EAG in Key Issue 11 of the EAR, data on age at NIV and age FVC <1L are not available for givinostat; these endpoints have not yet been reached within the clinical trial follow-up. Therefore, these timepoints are estimated by applying acceleration factors - derived from the UK registry study - to the age at LOA. As a result, both age at NIV and age at FVC <1L are dependent on age at LOA and the associated acceleration factor.<br><br>This means that applying hazard ratios for all three endpoints (LOA, NIV, and FVC <1L) directly to transition probabilities in the economic model would lead to an overestimation of the benefit of givinostat. Additionally, the model includes more granular health state transitions than these endpoints. For example, three states within the ambulatory phase, which means age at LOA encompasses transitions from health state 1 to 2, 2 to 3, and 3 to 4. Applying hazard ratios based on age at LOA for each of these more granular transitions would further overestimate the benefit of givinostat.<br><br>To avoid issues associated with overestimating the benefit of givinostat, the EAG has suggested applying the hazard ratio for age at LOA only within the economic model. This is only applied to the transition from health state 2 to 3.<br><br>From the Company's perspective, the EAG's approach underestimates the value of givinostat within the ambulatory health states - specifically in slowing disease progression between health states (e.g., from health state 1 to 2 and from 3 to 4) - as well as its effect on long-term clinical outcomes. Table O illustrates this by comparing the median ages at key disease milestones under the Company's base case and the EAG's preferred modelling approach. For the purposes of isolating the methodological differences in the economic models, both approaches use the same source of relative efficacy data i.e., the UK registry data. In the EAG's approach, a HR of 0.185 is applied to the transition from health state 2 to 3.<br><br>As shown in Table O, under the EAG's approach, no treatment benefit is assumed for the transition from health state 1 to 2. As a result, the median age at the milestone "unable to stand from supine" is identical for patients treated with givinostat and those treated with ECM. This is inconsistent with the treatment effect of givinostat on age at LOA.<br><br>To estimate the timing of longer-term disease milestones for patients treated with givinostat, the Company uses acceleration factors derived from the UK registry. Specifically:<br>• The ratio of median age at NIV to median age at LOA for ECM is 1.50 (18.46 / 12.28), which is applied as the acceleration | The EAG reiterate that, if a treatment effect for givinostat versus ECM is only believed to impact age at LOA (as stated by the company in responses to clarification questions), then it should only be applied to states relating to ambulation in the economic model. Subsequent to LOA, patients discontinue givinostat, so it is clinically reasonable to assume that no additional treatment effect occurs beyond this point, and to model this as such.<br><br>**Inappropriate assumptions when applying acceleration factors between givinostat and ECM**<br><br>The application of acceleration factors (AFs) to the givinostat data is inherently flawed:<br>• It actually *does* imply a treatment effect beyond LOA, even in the clinical evidence. This overestimates the efficacy of givinostat in the clinical evidence, and therefore also in the economic model (since the SOLVER HRs try to align the median age at endpoints to the clinical evidence).<br>• It assumes that AFs between outcomes are unchanged by treatment effect. If givinostat is expected to have a treatment effect on age at LOA then this is not mathematically justifiable (a HR of >1 or <1 at age at LOA would imply that AFs between time-to-event endpoints would be different in givinostat compared to in ECM)<br><br>To explain this in more detail, we have created an illustrative diagram (see Addendum to EAG Report: Section 2.7) to clarify this issue.<br><br>Furthermore, the company's approach hugely overcomplicates the fitting of givinostat data, since (beyond the issues with the unanchored ITC) it requires:<br>• Applying AFs estimated in ECM to the givinostat KM data (this makes the implausible assumptions described above)<br>• Fitting survival distributions to extrapolate givinostat KM data to estimate median time-to-event (this adds a completely unnecessary additional unnecessary layer of assumptions, when one could simply apply the AFs to the median age at LOA to get the median age at NIV and age at FVC<1L)<br>• Using SOLVER in Excel to solve for HRs that then seek to align a completely different natural history model to the weighted and extrapolated givinostat median time-to-event for each endpoint. This further assumes that the givinostat |

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| | | factor to derive median age at NIV for givinostat based on its estimated LOA.<br>• Similarly, the ratio for FVC <1L to LOA is 1.94 (23.86 / 12.28), and is used to estimate median age at FVC <1L for givinostat.<br>In the Company's base case, the resulting ratios for givinostat are consistent with these UK registry-based acceleration factors:<br>• NIV: 1.50 = 26.9 / 17.9<br>• FVC <1L: 1.94 = 34.7 / 17.9<br>This indicates that the effect of delaying LOA with givinostat is proportionally carried through to later-stage outcomes, in line with the real-world data observed for ECM.<br>Conversely, in the EAG's approach, the corresponding ratios for givinostat are significantly lower:<br>• NIV: 1.22 = 23.8/19.4<br>• FVC <1L: 1.45 = 28.1/19.4<br>This implies that, within the EAG's modelling framework, the delay in LOA for givinostat has a disproportionately smaller impact on long-term outcomes compared to ECM.<br>**Table O: Comparison of key milestones for ECM and givinostat under the Company and the EAG's preferred methodological approach**<br>Abbreviations: EAG, Evidence Assessment Group; ECM, established clinical management;.<br>As outlined in Section B.3.3.2 of the CS and in response to CQ B5 and B20, the Company acknowledges that directly applying HRs from the ITCs to the model would overestimate the benefit of givinostat. This is consistent with the EAG's critique in Key Issue 11 and is why HRs are not applied directly in the model.<br>Instead, the Company uses a SOLVER-based approach to estimate the HRs required to align the modelled median outcomes with those | and ECM arms used *in the model* are balanced in prognostic factors (i.e. in addition to assuming prognostic factors are balanced between the UK registry data for ECM and the EPIDYS/OLE data for givinostat data).<br>The EAG's proposed approach is simpler, makes fewer assumptions, and aligns with the company's stated belief as to where/when the treatment effect occurs. Transition probabilities to later states during ambulation (i.e. whilst on treatment) are reduced, so that patients progress through this part of the model more slowly. However, once they lose ambulation and progress to later states, they stop gaining any **further** benefit of Givinostat and so the transitions between these later states remain the same between ECM and givinostat.<br>The company is correct in stating that the delay in LOA for givinostat has a disproportionately smaller impact on long-term outcomes compared to ECM in the EAG's base case, but this is exactly what one would expect to see if there was a proportional treatment effect applied to age at LOA only.<br>The EAG's implementation still results in a marked increase in Age at LOA, Age at NIV and Age at FVC <1L in givinostat compared to ECM, but the increase is much less than the company's approach.<br>However, the transitions to which the EAG should apply the HR for age at LOA have been updated in the EAG's base-case model, to reflect all transitions where a treatment effect of givinostat versus ECM could be reasonably assumed to exist (i.e. whilst patients are still receiving givinostat). This applies to transitions 1 -> 2, 2 -> 3, and 3 -> 4, rather than just 2 -> 3. The effect of this is broadly similar to applying the HR to the full ambulatory Kaplan-Meier curve, rather than just the middle chunk of it. Results for this are given in the addendum to the EAG report. (Section 2.7).<br>**Use of AFs implies a treatment effect occurs in later health states, even in the clinical evidence, and overestimates the benefit of givinostat**<br>The EAG report stated that, whilst the way the HRs and treatment effect were applied in the economic model did not align with the company's belief regarding the treatment effect, the clinical evidence |

| Median age at: | ECM | Givinostat | EAG |
|---|---|---|---|
| Unable to stand from supine | 8.7 | 11.3 | 8.7 |
| Loss of ambulation | 12.1 | 17.9 | 19.4 |
| Loss of HTMF | 15.8 | 26.0 | 23.7 |
| Starting ventilation | 16.0 | 26.9 | 23.8 |
| Starting full-time ventilation | 20.3 | 34.8 | 28.1 |
| Death | 25.4 | 39.3 | 33.7 |

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| | | observed in the ITCs. This approach was discussed during the TE call, where it was acknowledged that the Company does not apply ITC-derived HRs directly. It was further clarified that the EAG's concern regarding potential "double counting" of treatment effect pertained to the scenarios conducted by the EAG, not the approach adopted by the Company.<br><br>Therefore, the Company considers its method of incorporating ITC data to be appropriate, avoiding double counting while enabling the generation of externally valid estimates of outcomes for givinostat. | for longer-term outcomes for givinostat (calculated using AFs) did still align with a treatment effect only applied to age at LOA:<br><br>*"When analysed independently it is therefore reasonable (albeit with the extensive limitations detailed in Section* ***Error! Reference source not found.****) to assume the use of acceleration factors in this way. However, the HRs estimated for each of the outcomes capture exactly the same mechanism for the treatment effect due to the way in which they are derived (from age at LOA in givinostat patients, using acceleration factors*).(Sections 4.2.6 and 6.1)"<br><br>However, having given further thought to the issue, the EAG now believe that the treatment effect is also inappropriately applied in the clinical evidence due to the use of acceleration factors, and that Kaplan-Meier data, median time-to-event and HRs for age at NIV and age at FVC <1L will overestimate the efficacy of givinostat. The Addendum to EAG Report: Section 2.7 provides further details to clarify this. |

# Additional issues

**All:** Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

**Table 3 Additional issues from the EAR**

| Issue from the EAR | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response | EAG response |
|---|---|---|---|---|
| **Additional issue 1:** Givinostat monitoring costs | Page 97, EAR | No | In the EAR, it is noted that clinical advice provided to the EAG indicated that monitoring costs related to givinostat would be relevant to NHS clinical practice. In response to CQ B8, we agreed with this assessment and referenced the SmPC for givinostat, which recommends regular monitoring of platelet counts and triglycerides to guide dosage adjustments. In our response, we included a scenario analysis based on non-consultant led monitoring. However, in the EAG's preferred base case, consultant-led monitoring costs are assumed. Based on feedback from clinicians throughout the NICE process, we anticipate that monitoring in clinical practice may involve a combination of non-consultant and consultant-led care. Nevertheless, we are prepared to proceed with the conservative assumption of consultant-led monitoring for givinostat, and these costs will be reflected in the updated cost-effectiveness results. | No new evidence provided. The EAG chose consultant led monitoring because of the complexity of this disease area. There are also other items which would be monitored which have not been modelled including endocrinology, so the EAG view is that costs are under rather than over estimated. |
| **Additional issue 2:** Givinostat hydrochloride versus givinostat free base case | Follow-up email from NICE (22nd April 2025)<br>• In the "Cost data" tab of the model Cells H48:56, mg refer to givinostat hydrochloride (10 mg/ml) derived from the | No | The Company submitted the EPIDYS dosing to both the EMA and the Food and Drug Administration (FDA). Givinostat received approval in the US for the treatment of patients with DMD on 21 March 2024, during the Day 120 clock stop for the Marketing Authorisation Application (MAA).<br>During the New Drug Application (NDA) review, the FDA raised concerns about the complexity of the dose/regimen dose instructions and about patients' exposures and dose related AEs (mainly thrombocytopaenia, hypertriglyceridaemia, gastrointestinal symptoms). In addition, the FDA noted that the pharmacometrics analyses presented in the NDA showed higher exposure in patients in the 60 to 70Kg weight band compared to lighter patients when receiving the same dose level. This led to an Information request requesting the Company to conduct pharmacometrics simulations (PK, PK-PD) to evaluate a potential | The EAG recognise the mismatch between the calculated dose (mg) and the cost inputs. The EAG have accepted this correction to the model and propagated to the preferred base case. |

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| | "Givinostat Dose calculation" tab. Whereas the mg/ml in Cell I48 refers to the free base (8.86 mg/ml)<br>• The per cycle costs in Column O combine mg of givinostat hydrochloride with the price per mg of the free base.<br>Please could you look into this possible error and correct if needed | | alternative dosing regimen, with a reduced number of weight bands, to be compared with the originally proposed dose regimen applied in EPIDYS.<br>In response to the request, the Company conducted the requested analysis evaluating the simplified dosing regimen that still achieves exposures equivalent to those observed in EPIDYS and further optimised the FDA revised dosing regimen, to decrease the likelihood of dose reductions due to platelet count reductions in the heavier weight bands (>40 kg). During the final stages of labelling discussions, the FDA proposed additional minor revisions to the initial dose reduction, to further reduce the risk of platelet count reductions in heavier patients. These analyses and discussions with the FDA led to the dose regimen now included in the givinostat USPI & UKPI. The revised dose regimen represents a simplification of the dosing instructions, leading to the use of only one oral syringe for the administration, and also addressing the FDA's concerns regarding the complexity of dosing.<br>In the economic model, dosing is derived from the volume (in mL) used in the EPIDYS clinical trial, and the corresponding dose in milligrams was calculated based on the 10 mg/mL concentration. As the NICE Team have highlighted, this approach is inconsistent with the commercially available 8.86 mg/mL formulation used to inform drug costs in the model. As a result, there is a mismatch between the calculated dose (mg) and the cost inputs. We have corrected this error as part of the changes to the cost-effectiveness results in this technical engagement response.<br>Table P presents the corrected Dose A, Dose B, and Dose C values from EPIDYS, updated using the 8.86 mg/mL concentration – these values replace the information on mg dosing from EPIDYS in Section B.2.3.1 and Appendix M.2 of the CS.<br>The correct text from Section B.2.3.1 should state, the initial doses of givinostat were based on a dose ranging evaluation in a mouse model,[28] in addition to the results of the previous Phase 2 study in boys with DMD[29] and several studies of other disorders.[30,31] A flexible treatment regimen was used, in which a fixed starting dose of givinostat was given to maximise efficacy but dose reductions were prespecified if AEs occurred, such as platelet count reduction or diarrhoea.[30,31] The weight-based starting dose was initially **2–7 mL (17.72–62.02 mg)** oral | |

givinostat twice a day, with a reduced dose of **1.3–4.7 mL (11.52–41.64 mg)** twice a day (see **Table P**, **Dose A and B in the "Givinostat Dose Calculation" sheet**). A protocol amendment following the masked safety review (in June 2018), reduced the starting dose to Regimen 2 (**Table P**) for boys who were recruited after the amendment. The starting dose for Regimen 2 was **1.3–4.7 mL (11.52–41.64 mg)** twice a day, with a reduced dose of **1.1–3.7 mL (9.75–32.78 mg)** twice a day (**Table P, Dose B and C in the "Givinostat Dose Calculation" sheet**). A subsequent protocol amendment, applying only to France, moved all boys to Regimen 2.[30,31] If boys gained weight during the study, the drug dose was kept unchanged; if boys lost weight the dose was adjusted as described in the CS.

These revised values have been incorporated into the cost-effectiveness model in the "Givinostat Dose Calculation" sheet. Table Q provides an update of Table 42 from the CS. This correction reduces the original base case ICER by 11.0%.

**Table P: Dose calculations informing the economic model**

| Weight | 10-12,5 Kg | 12.5-20 Kg | 20-25 Kg | 25-30 Kg | 30-40 Kg | 40-50 Kg | 50-60 Kg | 60-70 Kg | 70 Kg |
|---|---|---|---|---|---|---|---|---|---|
| **Dose A** | | | | | | | | | |
| Oral suspension (mL) | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 | 5.0 | 5.5 | 6.0 | 7.0 |
| Dose per day ml (A) | 4.0 | 5.0 | 6.0 | 7.0 | 8.0 | 10.0 | 11.0 | 12.0 | 14.0 |
| Dose per day mg (A) | 35.4 | 44.3 | 53.2 | 62.0 | 70.9 | 88.6 | 97.5 | 106.3 | 124.0 |
| **Dose B** | | | | | | | | | |
| Oral suspension (mL) | 1.3 | 1.7 | 2.0 | 2.3 | 2.7 | 3.3 | 3.7 | 4.0 | 4.7 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose per day ml (B) | 2.6 | 3.4 | 4.0 | 4.6 | 5.4 | 6.6 | 7.4 | 8.0 | 9.4 |
| Dose per day mg (B) | 23.0 | 30.1 | 35.4 | 40.8 | 47.8 | 58.5 | 65.6 | 70.9 | 83.3 |
| **Dose C** | | | | | | | | | |
| Oral suspension (mL) | 1.1 | 1.3 | 1.6 | 1.9 | 2.1 | 2.7 | 2.9 | 3.2 | 3.7 |
| Dose per day ml (C) | 2.2 | 2.6 | 3.2 | 3.8 | 4.2 | 5.4 | 5.8 | 6.4 | 7.4 |
| Dose per day mg (C) | 19.5 | 23.0 | 28.4 | 33.7 | 37.2 | 47.8 | 51.4 | 56.7 | 65.6 |

Abbreviations: kg, kilogram; mg, milligram; N, number

**Table Q: Number of patients receiving each of the weight-based dose distributions in the EPIDYS clinical trial and calculation of average weight-based dose distribution (updated Table 42 from CS)**

| **Weight** | **10-12.5 Kg** | **12.5-20 Kg** | **20-25 Kg** | **25-30 Kg** | **30-40 Kg** | **40-50 Kg** | **50-60 Kg** | **60-70 Kg** | **70 Kg** |
|---|---|---|---|---|---|---|---|---|---|
| Dose Regimen 1 starting dose, N (%) | 0 (0.0% | 7 (70.0%) | 15 (79.0%) | 18 (58.1%) | 6 (15.0%) | 1 (6.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dose Regimen 1 permitted dose reduction, N (%) | 0 (100.0%) | 1 (10.0%) | 2 (10.5%) | 10 (32.3%) | 23 (57.5%) | 10 (66.7%) | 1 (100.0%) | 2 (100.0%) | 0 (100.0%) |

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<tr><td>Dose Regimen 2, N (%)</td><td>0 (0.0%</td><td>2 (20. 0%)</td><td>2 (10. 5%)</td><td>3 (9.7 %)</td><td>11 (27. 5%)</td><td>4 (26. 7%)</td><td>0 (0.0 %)</td><td>0 (0.0 %)</td><td>0 (0.0 %)</td></tr>
<tr><td>Average dose per day (mg)</td><td>23.0</td><td>38.6</td><td>48.7</td><td>52.4</td><td>48.4</td><td>57.6</td><td>65.6</td><td>70.9</td><td>83.3</td></tr>
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Abbreviations: kg, kilogram; mg, milligram; N, number
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<td>Additional issue 3: Differences between trial and SmPC dosing</td>
<td>Follow-up email from NICE (22nd April 2025)<ul><li>The dosing regimens used in the trial are slightly different to those in the SmPC (Tables 1 & 2)</li><li>Please could you comment on any impact this might have on the estimates of cost-effectiveness</li></ul></td>
<td>No</td>
<td>The economic model applies the givinostat dosing regimen observed in the EPIDYS trial to ensure alignment with the source of efficacy data.<br><br>The SmPC provides updated dosing guidance informed by the outcomes of the EPIDYS trial. The dosing evolution for givinostat reflects a balance between maximising efficacy and managing safety. As no new safety concerns emerged during EPIDYS, the SmPC recommends slightly higher dosing than was used in the trial. As higher dosing may be associated with improved outcomes, it is reasonable to expect potential gains in effectiveness. However, to maintain consistency with the efficacy data that informs the economic model, the dosing used in EPIDYS is assumed to be representative of the dose linked to those outcomes.<br><br>However, unlike the fixed dosing in EPIDYS, the model incorporates dose adjustments based on patient weight over time. Weight data for boys aged 6–18 years are derived from growth charts published by the Royal College of Paediatrics and Child Health.[32] This approach may represent a conservative assumption, as it is possible that if dosing in EPIDYS had been adjusted for weight, additional gains in effectiveness could have been observed.</td>
<td>The EAG have accepted and followed the company dosing in the preferred base case.</td>
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<td>Additional issue 4: Wastage</td>
<td>Follow-up email from NICE (22nd April 2025)<ul><li>Current drug costs appear to be applied as a per cycle cost (i.e per</li></ul></td>
<td>No</td>
<td>Givinostat, as described in the SmPC and clinical practice, is formulated as an oral suspension supplied in bottles, each containing a defined amount of active ingredient. Dosing can be tailored to the individual, with the flexibility to use full or partial bottles as needed. Unopened bottles have a shelf life of three years, and once opened, the product remains usable for up to 60 days. In the event of a dose reduction, the remaining medication is not wasted but retained for future use, with clinicians simply delaying the next reorder. This flexible dosing approach differs</td>
<td>On the assumption that clinics can manage the described inventory, the EAG accept that wastage does not need to be modelled.</td>
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| | mg), after compliance/RDI and ignoring wastage (i.e if someone discontinues part way through a bottle).<br>• 3.5.6 of PMG24 states wastage should be taken into account.<br>• Please could you comment on this and on any impact this might have on estimates of cost-effectiveness as well as provide scenarios that could model/emulate wastage (e.g applying a fraction of the cost of a bottle at discontinuation) | | from drugs provided in fixed-dose vials or pre-filled syringes, where unused portions are often discarded. As a result, drug wastage is expected to be negligible, with doses prepared to match individual patient requirements. | |

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| **Additional issue 5:** Face validity of time on treatment | Follow-up email from NICE (22nd April 2025)<br>• Is there a plausible reason why discontinuation would be greater for givinostat + steroids (a more effective treatment) than steroids alone?<br>• Please could you comment on this | No | For clarity, in the economic model the discontinuation rate for steroids is assumed to be equal in both treatment arms. This is described in Section **Error! Reference source not found.** and Section B.3.3.4 of the CS, it is assumed that givinostat will not impact the CS use.<br>Nevertheless, the discontinuation rate for givinostat is modelled as higher than for corticosteroids alone, in line with EPIDYS trial data. Over the 18-month follow-up, 5.9% of patients in the givinostat arm discontinued treatment, compared with 3.3% in the placebo arm. In EPIDYS, givinostat was administered in addition to CS, and it is assumed that NICE's question refers to this combination. While this difference is relatively small, it may reflect the added burden of combination therapy. Although givinostat is generally well tolerated, its use alongside steroids introduces additional side effects that may contribute to a modestly higher discontinuation rate. This may contribute to the observed difference in discontinuation rates. | EAG clinical advice agreed that there would be more side effects on givinostat but that the data from the company study suggests that discontinuation is not that much higher (even though side effects were). |
| **Additional issue 6:** Model starting age | Follow-up email from NICE (22nd April 2025)<br>• Currently set to 6 years, lowest age in the MA, reflects the incident age<br>• Should the prevalent age be explored? Mean age in the trial was closer to 10 years<br>• Please could you comment | No | The economic model begins at age six, consistent with the SmPC for givinostat, which specifies use in boys aged six years and older. This starting age also aligns with the EPIDYS clinical trial, which enrolled boys aged at least 6 years. By modelling from age six, the population reflects the earliest point of trial eligibility and aligns with the intended treatment population in UK clinical practice.<br>In DMD, earlier treatment is known to accrue greater benefits in preserving muscle function and delaying disease progression. Although the mean age in the EPIDYS trial was 9.8 years (Overall ITT population) in the givinostat arm, in UK clinical practice givinostat is expected to be initiated at the earliest opportunity i.e., when boys become eligible at age six. Starting treatment earlier than observed in EPIDYS will likely result in better preservation of mobility and function than observed in the trial population. Therefore, the EPIDYS data used in the model likely underestimates the full potential benefits of givinostat given from age six. | The EAG agree with the company and have kept the model starting age at 6 years old. The EAG agrees that EPIDYS may underestimate treatment benefit (though the extent is unknown). |

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| | on this, which age should be modelled and used for decision making | | | |
| **Additional issue 7:** Application of severity modifier | Follow-up email from NICE (22nd April 2025)<br>• Please could you ensure that the severity modifier is only applied to patient incremental QALYs for all estimates of cost-effectiveness presented. | No | This is reflected in our changes to the Company's cost-effectiveness results. | The EAG view that the company have estimated this correctly for their base case, by applying the severity modifier to the patient QALYs and adding in the carer QALYs unmodified. |

# Summary of changes to the company's cost-effectiveness estimate(s)

In the revised base case and as part of the TE process, an updated PAS for givinostat has been submitted. A simple PAS of [redacted]% is applied to the cost of givinostat which reduces the cost per 8.86 mg/mL 140 mL bottle from £13,846 to £[redacted].

In addition to the updated PAS, a number of changes have been made in response to issues raised in the EAR and throughout TE. Table 4 reflects the changes from the original base case to the revised base case. Table 5 presents the revised base case results with the updated PAS.

**Table 4: Changes to the company's cost-effectiveness estimate**

| Key issue(s) in the EAR that the change relates to | Company's base case before technical engagement | Change(s) made in response to technical engagement | Impact on the company's base-case incremental cost-effectiveness ratio (ICER) |
|---|---|---|---|
| Additional issues, Scenario 7 in EAR | Givinostat monitoring costs: excluded | Givinostat monitoring costs: included as per EAG's base case | Original base case ICER: £141,583. Inclusion of givinostat monitoring costs as per EAG base case: £142,098 (+0.36%) |
| Additional issues, givinostat dosing | Givinostat dosing calculations: based on 10 mg/mL. Not aligned with the bottle size and costing | Givinostat dosing calculations: based on 8.86 mg/mL. Aligned with the bottle size and costing. | Original base case ICER: £141,583. Update to 8.86mg/mL bottle size: £125,999 (-11.01%) |
| Additional issues, severity modifier | Severity modifier: applied to incremental patient and caregiver QALYs | Severity modifier: applied to incremental patient QALYs | Original base case ICER: £141,583. Apply severity modifier to incremental patient QALYs only: £198,503 (+40.20%) |
| Company's base case following technical engagement (or revised base case) | Incremental QALYs: 15.98 | Incremental costs: £2,835,222 (excluding PAS), £[redacted] (including updated PAS) | Revised base-case ICER: £177,377 (+25.28% from original base case ICER; excluding PAS), £[redacted] (including updated PAS) |

**Table 5: Revised base case results (with updated PAS)**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs* | ICER (£/QALY)* |
|---|---|---|---|---|---|
| **Givinostat** | £[redacted] | 19.33 | | | |
| **ECM** | £99,448 | 6.14 | £[redacted] | 15.98 | £[redacted] |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.
*Including the 1.7 severity modifier, applied to incremental patient QALYs only

**Sensitivity analyses around revised base case**

The probabilistic (PSA) and one-way sensitivity analyses (OWSA) have been updated in line with the revised base case and the updated PAS.

Table6 presents the probabilistic results. The probabilistic ICER is £[redacted]. This is congruent with the deterministic ICER of £[redacted], as demonstrated by the overlap in markers showing the deterministic and probabilistic base case in the cost-effectiveness plane (Figure 1). The CEAC is depicted in Figure 2. The proportion of simulations considered cost-effective at a threshold of £30,000 and £50,000 are [redacted]% and [redacted]%, respectively.

**Table 6: Probabilistic results (with updated PAS) | Revised base case**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs* | Probabilistic ICER (£/QALY)* | Deterministic ICER (£/QALY)* |
|---|---|---|---|---|---|---|
| **Givinostat** | £[redacted] | 19.64 | | | | |
| **ECM** | £99,086 | 6.17 | £[redacted] | 16.35 | £[redacted] | £[redacted] |

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year.
*Including the 1.7 severity modifier, applied to incremental patient QALYs only.

**Figure 1: Cost-effectiveness plane | Revised base case | 1,000 iterations (with updated PAS)**



Abbreviations: PAS, patient access scheme; QALY, quality adjusted life year

**Figure 2: Cost-effectiveness acceptability curve | Revised base case | 1,000 iterations (with updated PAS)**



Abbreviations: NMB, net monetary benefit; PAS, patient access scheme

Results for the ten most influential parameters are depicted in a tornado diagram in Figure 3 and detailed in Table 7 using the ICER as the outcome and applying the updated PAS for givinostat. The interpretation through which the parameters impact the cost-effectiveness results remains aligned with that described in the original CS (Section B.3.11.2).

**Figure 3: Tornado diagram | Revised base case | ICER (with updated PAS)**



Abbreviations: HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

**Table 7: One-way sensitivity analysis (with updated PAS) | Revised base case**

| Parameter | ICER at upper value of parameter | ICER at lower value of parameter |
|---|---|---|
| Number of caregivers | [redacted] | [redacted] |
| Givinostat HR: To state 2 - Late ambulatory | [redacted] | [redacted] |
| Number of patients discontinuing givinostat - OLE | [redacted] | [redacted] |
| Givinostat HR: To state 3 - Transfer | [redacted] | [redacted] |
| Average weight: Age 18 | [redacted] | [redacted] |
| Givinostat number with dose modifications - OLE | [redacted] | [redacted] |
| Patient utilities: health state 1 - Early ambulatory | [redacted] | [redacted] |
| Givinostat HR: To state 4 - HTMF, no ventilation | [redacted] | [redacted] |
| Givinostat HR: To state 7a - No HTMF, night-time ventilation | [redacted] | [redacted] |
| Caregiver utilities: health state 1 - Early ambulatory | [redacted] | [redacted] |

Abbreviations: HR, hazard ratio; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

Table 8 presents the deterministic scenario analyses for the revised base case with the updated PAS. These results update those presented in Table 95 in the CS. Additionally, in response to Key Issue 8 i.e. “Costs and quality of life assumed the same in the full ventilation states and night ventilation states” two additional scenarios are presented reflecting the Company’s response to exploring this assumption and the EAG’s response to exploring this assumption – both scenarios indicate the base case ICER may be conservative.

**Table 8: Deterministic scenario analyses (with updated PAS) | Revised base case**

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | % change from base-case ICER |
|---|---|---|---|---|
| Base-case | [redacted] | 16.0 | [redacted] | 0.0% |
| **Key issue 3:** inclusion of all givinostat patients in the MAICs | [redacted] | 16.28 | [redacted] | -1.68% |
| **Key issue 8:** Company approach i.e., multiplier in health state 8 | [redacted] | 15.98 | [redacted] | -0.73% |
| **Key issue 8:** EAG approach i.e., BOI source for costs and patient utilities | [redacted] | 16.55 | [redacted] | -1.87% |
| Time horizon: 50 years | [redacted] | 15.0 | [redacted] | 5.8% |
| Time horizon: 60 years | [redacted] | 15.7 | [redacted] | 1.6% |
| Perspective: Societal using Landfeldt et al. | [redacted] | 16.0 | [redacted] | 17.2% |
| Perspective: Societal using Project HERCULES BOI | [redacted] | 16.0 | [redacted] | 16.6% |
| Discount rates: 3.5% costs and 1.5% outcomes across model time horizon | [redacted] | 19.7 | [redacted] | -19.1% |
| Distribution and dosing schedule for CS: UK real-world data | [redacted] | 16.0 | [redacted] | 1.2% |
| NHM: Updated analysis 1 | [redacted] | 20.2 | [redacted] | -17.1% |
| NHM: Original | [redacted] | 15.9 | [redacted] | 4.7% |
| Source for treatment duration, adverse events, compliance, and dose modifications: EPIDYS | [redacted] | 16.0 | [redacted] | -9.0% |
| Givinostat continuation rule: until fulltime ventilation | [redacted] | 16.0 | [redacted] | -4.5% |
| Givinostat continuation rule: until loss of HTMF | [redacted] | 16.0 | [redacted] | -19.0% |
| Givinostat continuation rule: until loss of ambulation | [redacted] | 16.0 | [redacted] | -39.9% |
| CS continuation rule: until fulltime ventilation | [redacted] | 16.0 | [redacted] | 0.0% |
| CS continuation rule: until loss of HTMF | [redacted] | 16.0 | [redacted] | -0.4% |
| CS continuation rule: until loss of ambulation | [redacted] | 16.0 | [redacted] | -0.9% |

| | | | | |
|---|---|---|---|---|
| Patient utilities: Landfeldt et al. | [redacted] | 15.2 | [redacted] | 4.8% |
| Patient utilities: Project HERCULES BOI | [redacted] | 16.5 | [redacted] | -3.4% |
| Number of caregivers: three | [redacted] | 16.0 | [redacted] | 0.0% |
| Caregiver utilities: Landfeldt et al. | [redacted] | 16.0 | [redacted] | 0.0% |
| Caregiver HRQoL approach: utilities | [redacted] | 16.0 | [redacted] | 0.0% |
| Caregiver HRQoL approach: disutilities | [redacted] | 8.1 | [redacted] | 97.1% |
| Caregiver HRQoL approach: increments relative to severe | [redacted] | 8.1 | [redacted] | 97.1% |
| Health state costs: Landfeldt et al. | [redacted] | 8.1 | [redacted] | 97.1% |
| Health state costs: Project HERCULES BOI | [redacted] | 16.0 | [redacted] | 6.3% |

Abbreviations: BOI, burden of illness; CS, corticosteroids; ECM, established clinical management; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; NHM, natural history model; OLE, open-label extension; PAS, patient access scheme.

# Appendix

## Selection of evidence to support indirect treatment comparison

The published UK real-world data source, i.e. North Star data from three centres presented by Pietrusz[3,4], is the most appropriate data source when estimating the efficacy of patients receiving ECM, as this reflects both the UK DMD population and UK clinical practice.

This dataset is preferred compared with alternative UK and non-UK datasets due to:

- Timing of data collection (published in 2023/2024)
- Availability of Kaplan-Meier curves for multiple ambulatory and non-ambulatory outcomes, ensuring a consistent dataset can be included across outcomes when conducting the unanchored MAICs

Note that no access to individual patient-level data (IPD) was available for any study for established clinical management (ECM). Appendix Table 1 summarises at a topline level the rationale for selecting the RWE data sources for the ITC. Appendix Table 2 provides more detailed reasons for inclusion or exclusion of each potential source identified by the SLR.

### Appendix Table 1: Summary of potential alternative ECM data sources

| | Notes | Versus UK real-world data source |
|---|---|---|
| CINRG subset from research comparing patients receiving ECM with STRIDE registry data[6] | • Included in givinostat MAIC SA<br>• Included in NICE HST appraisal 22 to form an ITC comparing ataluren with ECM | • Data not as recent as the UK real-world data (patients recruited during 2 time periods: 2006–09 and 2012–16)<br>• Study was not conducted in UK centres |
| CINRG full population[33] | Excluded from analyses | • As per CINRG subset, older data and no UK centres<br>• In addition, some boys had participated in clinical trials of ataluren or had received eteplirsen, drisapersen or tadalafil; or they had missing data for age at LOA and age at first symptoms. These patients were excluded in the CINRG subgroup used for the givinostat MAIC SA (data reported in Mercuri 2023[6]) |
| North Star dataset for larger number of included centres, for example as reported in Zambon 2022,[16] and Stimpson 2024[17] | Excluded from analyses | • KM curves only available for ambulatory outcomes and not across multiple ambulatory and non-ambulatory outcomes<br>• Pick-and-mix of different cohorts of North Star patients and cut off dates would be required to include this data in the MAICs, with the potential to yield inconsistent findings across disease milestones |

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; ECM, established clinical management; HST, highly specialised technology; ITC, indirect treatment comparison; K-M, Kaplan-Meier; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; SA, sensitivity analysis; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

## Appendix Table 2: List of studies included in the clinical SLR based on the PICOS criteria relevant to the decision problem

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| **Givinostat studies** | | | | |
| E. Mercuri; J. J. Vilchez; O. Boespflug-Tanguy; et al. | 2024 | Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial | Not applicable – givinostat publication | The Company included all givinostat clinical trial studies for which patient-level data were available to inform the givinostat arm in the ITC (EPIDYS; Study 43; Study 51). These studies are not relevant for identifying ECM comparator data with a long follow up period (>18 months) |
| Eugenio Maria Mercuri, Claudia Brogna, Craig Zaidman, Katherine Mathews, et al. | 2024 | M163: The EPIDYS Givinostat Study in DMD: supportive results | Not applicable – givinostat publication | As above |
| Simonetta Andrea Licandro, Stefania Petrini, Krista Vandenborne, et al. | 2024 | S71: Givinostat effects on DMD pathogenesis | Not applicable – givinostat publication | As above |
| C. Mcdonald, L. Servais, F. Munell, et al. | 2024 | P369: Givinostat in Duchenne muscular dystrophy: effect on disease milestones | Not applicable – givinostat publication | As above |
| K. Vanderborne, R. Willcocks, G. Walter, et al. | 2024 | P370: Givinostat in DMD: results of the EPIDYS Study with particular attention to MR measures of muscle fat fraction | Not applicable – givinostat publication | As above |
| E. Mercuri, C. Brogna, J. Mah, et al. | 2024 | P371: Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA | Not applicable – givinostat publication | As above |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| K. Vandenborne; R. Willcocks; G. Walter; et al. | 2023 | Givinostat in DMD: results of the EPIDYS study with particular attention to MR measures of muscle fat fraction | Not applicable – givinostat publication | As above |
| E. Mercuri; C. Brogna; J. Mah; et al. | 2023 | Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA | Not applicable – givinostat publication | As above |
| C. McDonald; L. Servais; F. Munell; et al. | 2023 | Givinostat in Duchenne muscular dystrophy: effect on disease milestones | Not applicable – givinostat publication | As above |
| Eugenio Mercuri, Claudia Brogna, Jean K. Mah, et al. | 2023 | P99: Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA | Not applicable – givinostat publication | As above |
| Krista Vandenborne, Rebecca Willcocks, Glenn Walter, et al. | 2023 | P113: Givinostat in DMD: results of the EPIDYS Study with particular attention to MR measures of muscle fat fraction | Not applicable – givinostat publication | As above |
| E. Mercuri; J. Vilchez; O. Boespflug-Tanguy; et al. | 2022 | O.13 Givinostat in DMD: results of the EPIDYS Study | Not applicable – givinostat publication | As above |
| Paolo Umberto Bettica | 2022 | Update on the development of Givinostat in DMD | Not applicable – givinostat publication | As above |
| **Natural history studies** | | | | |
| Pietrusz A, Astin R, Guglieri M, et al. | 2024 | P39 The effect of corticosteroid treatment on pulmonary function in adults with Duchenne muscular dystrophy | Yes | Included in base case, multiple outcomes of interest reported for a UK cohort |
| Pietrusz A | NR | Natural history of DMD cohort attending Neuromuscular Service National Hospital for | Yes | Included, publication linked with study in row above |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| | | Neurology and Neurosurgery, Queen Square, London | | |
| Christian Werner, Shiwen Wu, Sheffali Gulati, et al. | 2024 | M166: Ataluren delays clinically meaningful milestones of decline in 6MWD in patients with nmDMD from Study 041, a phase 3, placebo-controlled trial | Ataluren study | Trial includes placebo arm but only short-term follow-up (72 weeks only) |
| Christian Werner, Eugenio Maria Mercuri, Francesco Muntoni, et al. | 2024 | T328: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Christian Werner, Már Tulinius, Filippo Buccella, et al. | 2024 | T327: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| G. Stimpson; D. Ridout; A. Wolfe; E. Milev; E. O'Reilly; A. Manzur; A. Sarkozy; F. Muntoni; T. J. Cole; G. Baranello | 2024 | Quantifying Variability in Motor Function in Duchenne Muscular Dystrophy: UK Centiles for the NorthStar Ambulatory Assessment, 10 m Walk Run Velocity and Rise from Floor Velocity in GC Treated Boys | Participants from the UK NorthStar registry | Outcomes not of interest for economic model and no baseline characteristics reported; includes assessment only up to 16 years (when boys start to transition to adult services) |
| E. Mercuri; F. Muntoni; F. Buccella; et al. | 2023 | Age at loss of ambulation in patients with DMD from the STRIDE registry and the CINRG natural history study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| E. Mercuri; A. N. Osorio; F. Muntoni; et al. | 2023 | Correction to: Safety and effectiveness of ataluren in patients with nonsense mutation DMD in the STRIDE Registry compared with the CINRG Duchenne Natural History Study (2015-2022): 2022 interim analysis | Yes. STRIDE vs CINRG | Erratum to main paper that is included in the ITC (see below) |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| J. Broomfield; K. Abrams; N. Latimer; et al. | 2023 | Natural history of Duchenne muscular dystrophy in the United Kingdom: A descriptive study using the Clinical Practice Research Datalink | CPRD (Clinical Practice Research Database): GOLD and Aurum | No baseline characteristic data available; no outcomes of interest |
| V. Laugel; S. D. Lucia; J. Davion; et al. | 2023 | Preliminary Results from a Prospective, Multicentric, Follow Up Standardized Cohort to Assess Natural History of Duchenne muscular dystrophy | The analysis includes 48 patients with at least 6 months follow up (mean=13.5 months) from France and UK | Conference abstract with insufficient detail |
| M. Tulinius; F. Buccella; I. Desguerre; et al. | 2023 | Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE registry and CINRG natural history study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| E. Mercuri; A. N. Osorio; F. Muntoni; et al. | 2023 | Safety and effectiveness of ataluren in patients with nonsense mutation DMD in the STRIDE Registry compared with the CINRG Duchenne Natural History Study (2015-2022): 2022 interim analysis | Yes. STRIDE vs CINRG | Included in ITC, multiple outcomes of interest reported for the subgroup of CINRG patients |
| Pannie (Panayiota) Trifillis, Eugenio Mercuri, Francesco Muntoni, et al. | 2023 | P186: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Christian Werner, Már Tulinius, Filippo Buccella, et al. | 2023 | P116: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Christian Werner, Már Tulinius, Filippo Buccella, et al. | 2023 | EPNS23-2070: Pulmonary function in patients with Duchenne muscular dystrophy from the | STRIDE vs CINRG | Conference abstract with insufficient detail |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| | | STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | | |
| Panayiota Trifillis, Eugenio Mercuri, Francesco Muntoni, et al. | 2023 | EPNS23-2064: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis | STRIDE VS CINRG | Conference abstract with insufficient detail |
| C. M. McDonald; F. Muntoni; V. Penematsa; et al. | 2022 | Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients | Study 019 (ataluren) vs CINRG | Small subgroup of CINRG patients matched with ataluren Study 019; Mercuri 2023 CINRG dataset preferred due to larger number of included patients |
| D. Machado; E. de Paula; T. Márcia; et al. | 2022 | CO105 Long-Term Benefit of Ataluren Treatment in Non-Sense Duchenne muscular dystrophy Versus Standard of Care | Ataluren (STRIDE vs CINRG and Study 019 vs CINRG) | Conference abstract with insufficient detail |
| Pannie Trifillis, Francesco Muntoni, Már Tulinius, et al. | 2022 | P98: Comparison of North Star Ambulatory Assessment score change in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial | STRIDE vs Study 020 NCT01826487 | Conference abstract with insufficient detail |
| E. Mercuri; F. Muntoni; F. Buccella; et al. | 2022 | P22: Age at loss of ambulation in patients with DMD from the STRIDE registry and the CINRG natural history study: A matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Pannie Trifillis, Eugenio Mercuri, Francesco Muntoni, et al. | 2022 | P97: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| Pannie Trifillis, Már Tulinius, Filippo Buccella, et al. | 2022 | P99: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| Craig McDonald, Claudio L. Santos, Rich Able, et al. | 2022 | P110: Associations Between Daily Deflazacort or Prednisone and Ages at Disease Progression Milestones Among Patients with Duchenne muscular dystrophy (DMD) | PRO-DMD-01 and CINRG natural history studies | Conference abstract with insufficient detail |
| M. Tulinius; F. Buccella; I. Desguerre; et al. | 2022 | P.23 Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis | STRIDE vs CINRG | Conference abstract with insufficient detail |
| A. A. Zambon; V. Ayyar Gupta; D. Ridout; et al. | 2022 | Peak functional ability and age at loss of ambulation in Duchenne muscular dystrophy | UK NorthStar Network | Only ambulation-related outcomes reported; thus Pietrusz subgroup preferred as a consistent set of data reporting both LOA and respiratory outcomes |
| E. Mercuri; F. Muntoni; A. N. Osorio; et al. | 2020 | Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study | STRIDE vs CINRG | Contains subgroup of dataset reported in Mercuri 2023 that was included in the ITC (STRIDE vs CINRG) |
| C. M. McDonald; H. Gordish-Dressman; E. K. Henricson; et al. | 2018 | Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history with and without glucocorticoids | CINRG alone (GC > 1 year vs GC naïve) | Outcomes of interest not reported |
| C. M. McDonald; E. K. Henricson; R. T. Abresch; et al. | 2018 | Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study | CINRG (NCT 00468832) | Subgroup of CINRG patients reported in Mercuri 2023 preferred as some restrictions applied to the Mercuri dataset, which enabled a more balanced comparison with the givinostat data. For example, 22 CINRG patients were excluded because they had participated in clinical trials of ataluren or had received eteplirsen, drisapersen or tadalafil; 20 patients were also excluded because they had missing data for age at loss of ambulation and age at first symptoms |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| V. Ricotti; D. A. Ridout; M. Pane; et al. | 2016 | The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials | UK NorthStar Network + data from 172 Italian boys with DMD | Outcomes not of interest; no Kaplan-Meier curve for age at LOA |
| L. Bello; H. Gordish-Dressman; L. P. Morgenroth; et al. | 2015 | Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study | CINRG-DNHS | Outcomes not of interest (LOA by steroid regimen for all enrolled CINRG patients) |
| G. Schram; A. Fournier; H. Leduc; et al. | 2013 | All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy | Retrospective cohort study on patients with DMD treated with renin-angiotensin-aldosterone system antagonists with or without steroid therapy | Outcomes not of interest (mortality and CV events) |
| V. Ricotti; D. A. Ridout; E. Scott; et al. | 2013 | Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy | NorthStar UK database (17 neuromuscular centres in the UK) | Only ambulation-related outcomes considered; thus Pietrusz subgroup preferred as a consistent set of data reporting both LOA and respiratory outcomes and reports more recently collected data, and therefore more likely to reflect current treatment practise |
| C. M. McDonald; E. K. Henricson; R. T. Abresch; et al. | 2013 | The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study | The natural history data were derived from the placebo arm of a phase 2b, international, multicentre, randomised, double-blind, placebo-controlled, dose- | Short follow-up, 48 weeks only |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| | | | ranging study to evaluate the efficacy and safety of ataluren in ambulatory male patients aged ≥5 years with nonsense mutation DMD | |
| E. K. Henricson; R. T. Abresch; A. Cnaan; et al. | 2013 | The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures | CINRG | No outcomes of interest; short follow-up, 12 months only |
| **Update review (November 2024)** | | | | |
| **Givinostat** | | | | |
| D. Vučinić; A. Nascimento; R. Finkel; et al. | 2024 | Short-term and long-term safety profile of Givinostat in Duchenne muscular dystrophy | Not applicable – givinostat publication | The Company included all givinostat clinical trial studies for which patient-level data were available to inform the givinostat arm in the ITC (EPIDYS; Study 43; Study 51). These studies are not relevant for identifying ECM comparator data with a long follow up period (>18 months) |
| D.G. Andres; V. Sansone; H. Phan; et al. | 2024 | Givinostat in Duchenne muscular dystrophy: natural history comparison applying propensity score matching | Not applicable – givinostat publication | As above |
| **Natural history** | | | | |

| Authors | Year | Title | Relevant RWE for ITC? | Notes |
|---|---|---|---|---|
| **Original SLR (May 2024)** | | | | |
| G. Stimpson: D. Ridout; A. Sarkozy; A. Manzur; et al. | 2024 | Relationship between growth and ambulation loss in Duchenne muscular dystrophy boys on steroids | UK NorthStar database | Age at LOA only outcome of interest reported; thus Pietrusz subgroup preferred as a consistent set of data reporting both LOA and respiratory outcomes |
| M. Van Der Holst; M. Italianer; A Wolfe; et al. | 2024 | Is upper extremity contracture progression related to changes in upper extremity function in Duchenne muscular dystrophy? An international multicenter natural history study | International multicentre natural history study | Conference abstract with insufficient detail |
| V. Laugel; A. Seferian; J.B. Davion; et al. | 2024 | Preliminary results from a prospective, multicentric, follow up standardized cohort to assess natural history of Duchenne muscular dystrophy | France and UK natural history data (48 patients) | Conference abstract with insufficient detail |

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; GC, glucocorticoid; MR, magnetic resonance; nm, nonsense mutation; MR, magnetic resonance; NR, not reported; NSAA, North Star Ambulatory Assessment; SLR, systematic literature review; STRIDE, Strategic Targeting of Registries and International Database of Excellence; UK, United Kingdom.

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**Single Technology Appraisal**

**Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]**

**EAG report – factual accuracy check and confidential information check**

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 10 June 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

**Issue 1 Factual inaccuracies**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Page 8 of the EAG addendum: "However, for estimating comparative treatment efficacy by matching to EPIDYS/OLE (the unanchored ITC), **this source of evidence is poorly aligned**."<br><br>Page 15 of the EAG critique of company DG response: "However, for estimating comparative treatment efficacy by matching to EPIDYS/OLE (the unanchored ITC), **this source of evidence is poorly aligned**."<br><br>The EAG is correct that the UK Registry data does not include prognostic factors with which to match to the EPIDYS trial population. However, it does not | ITF requests that the EAG adapts its wording through the report to clarify that it is not possible to assess the degree of matching between EPIDYS and the UK registry. For example:<br><br>"However, for estimating comparative treatment efficacy by matching to EPIDYS/OLE (the unanchored ITC), **it is not possible to assess alignment due to a lack of matching criteria**." | It is not factually accurate to categorically state "poor alignment", when in fact there is simply a lack of evidence to assess alignment. | The EAG believe that there is sufficient evidence to be able to state that EPIDYS/OLE is poorly aligned to the UK registry study. The EPIDYS/OLE inclusion/exclusion criteria are more specific than would be expected in practice. Participants in EPIDYS/OLE have been enrolled in a trial and are under observation, and this is known to lead to performance bias.<br><br>If using uITC to match trial to trial, or registry to registry, then it may be reasonable to state that it is not possible to |

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| necessarily follow that this means that the populations are poorly matched. In fact, there are not sufficient data to assess the matching, as the EAG itself states. | | | assess alignment, but in this case (trial matched to registry) this is not the case.<br><br>Whilst it would not be fair to state with great confidence that one registry source for ECM should be preferred over the other (e.g. CINRGH DHNS vs UK registry), the EAG do believe that it is reasonable to state that, for assessing comparative treatment efficacy, both would be poorly aligned with EPIDYS/OLE. |
| Page 12 of the EAG addendum: “The EAG’s method is to calculate the caregiver utility decrements relative to the utility values for carers in the least sever | Unless it has been overlooked, the committee in TA1031 did not explicitly state a preference for the utility decrements approach; rather, this was simply the method they employed. However, there was considerable | It is not factually accurate to state that the committee in TA1031 preferred the utility decrements approach. | The EAG believe that this is semantic. The company chose this approach as it was their preferred method. |

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| state is a common method in appraisals of this disease area **and was preferred by the committee in TA1031**."<br><br>Page 30 of the EAG critique of company DG response: "The EAG's method is to calculate the caregiver utility decrements relative to the utility values for carers in the least sever state is a common method in appraisals of this disease area **and was preferred by the committee in TA1031.**" | ongoing discussion regarding the source of the values used to inform this approach. In this appraisal, the choice of method had less influence on the overall results, as vamorolone is not expected to have an impact on survival. | | As a compromise, we have edited in the EAG addendum to state that it was **selected by the committee in TA1031**. |
| Table 9, Page 20 of the EAG addendum: "Company's base-case + S1 + S3 + S4 + S5 +EAG's preferred assumption S6: Utilities and costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")" and Table 10, Page 22: "Company's base-case + S1 + S3 + S4 + S5 +EAG's preferred | Elsewhere in the report, the EAG state that<br><br>• Page 14: *"The EAG agrees with the company that quantifying the costs of medical aids required by disabled patients at the more severe health states by using a multiplier was not robust and thus no longer use it. The EAG agree with the company, costs derived from the Morgan et al. (2024) are suitable for decision making and used in the model as* | Please clarify which statements reflect the EAG base case and align across the report. | The key issue persists and the EAG prefers costs and utilities that distinguish between the full ventilation states and the night time states.<br><br>However, the EAG recognise the limitations with the available evidence, therefore the wording in tables 8 and 9 has been |

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| assumption S6: Utilities and costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")." | *presented in Addendum Table 7."*<br>• Table 8, page 18: *"The EAG have adopted direct medical costs from the company's base case, the HERCULES CPRD study by Morgan et al without the multiplier applied to direct costs. The EAG have kept the prior BOI source for utilities*."<br>The labelling in Table 9 does not align with these statements as the costs derived from Morgan et al. (2024) do not distinguish between health states 8 and 7. | | amended to clarify that only utilities distinguish between the full ventilation and night ventilation state. |
| Table 10, Page 22 of the EAG addendum: "Company's base-case + S1 + S3 + S4 + S5 + EAG's TE Scenario 1: Applying the age at LOA HR 469 (0.257, 0.855) with post-hoc selected givinostat matched to CINRG DHNS) to transitions 1->2, 2->3 and 3->4 rather than just 2->3." | The company has re-run the probabilistic analysis in the EAG's model, with the EAG's base case i.e., corresponding to a deterministic ICER of [redacted]. In the version of the model shared with the company, the corresponding probabilistic ICER is [redacted]. This differs substantially to the ICER presented by the EAG in Table 10 of the EAG addendum ([redacted]). | Please clarify the source of the [redacted] ICER or update this with the correct number. | The EAG thank the company for identifying this inconsistency. The ICER values have been corrected. |

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| The probabilistic ICER is reported to be [redacted]. This does not correspond with the deterministic ICER, nor does it correspond to the probabilistic incremental costs and QALYs presented in Table 10 of the EAG addendum i.e., [redacted] divided by 2.87. | | | |

**Issue 2 Confidentiality marking**

| Location of incorrect marking | Description of incorrect marking | Justification for amendment |
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| Page 60 of the EAG critique of company DG response: "The proportion of simulations considered cost-effective at a threshold of £30,000 and £50,000 are [redacted] and [redacted], respectively." | "The proportion of simulations considered cost-effective at a threshold of £30,000 and £50,000 are [redacted] and [redacted] respectively." | PAS is confidential. |

**Issue 3 Typographical errors**

| Description of problem | Description of proposed amendment | Justification for amendment |
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| Incorrect spelling on page 1 of the EAG critique of company DG response: | "Vamorolone is a corticosteroid and, therefore, has the potential to displace prednisone/prednisolone or **deflazacort** as a component of ECM." | To correct a spelling error. |

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| “Vamorolone is a corticosteroid and, therefore, has the potential to displace prednisone/prednisolone or **deflazacourt** as a component of ECM.”<br><br>“TA1031 considered vamorolone to have a more favourable side effect profile than prednisone or **deflazacourt**.” | “TA1031 considered vamorolone to have a more favourable side effect profile than prednisone or **deflazacort**.” | |
| Typographical error on page 16 of the EAG critique of company DG response: “The EAG therefore do not believe that matching trial data to either of these observational evidence sources is likely to be robust but given the limitations of **both the** EAG continue to believe that the CINRG DHNS dataset is likely to more closely match EPIDYS/OLE due to the greater potential to match on observed prognostic factors known to be important.” | “The EAG therefore do not believe that matching trial data to either of these observational evidence sources is likely to be robust but given the limitations of both**. T**he EAG continue to believe that the CINRG DHNS dataset is likely to more closely match EPIDYS/OLE due to the greater potential to match on observed prognostic factors known to be important.” | To correct an assumed grammar error/missing full stop. |
| Typographical error<br><br>Page 12 of the EAG addendum, methods for calculating the utility increments / decrements: “The | “The EAG’s method is to calculate the caregiver utility decrements relative to the utility values for carers in the least **severe** state is a common | To correct a spelling error. |

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| EAG's method is to calculate the caregiver utility decrements relative to the utility values for carers in the least **sever** state is a common method in appraisals of this disease area and was preferred by the committee in TA1031."<br><br>Page 30 of the EAG critique of company DG response: "The EAG's method is to calculate the caregiver utility decrements relative to the utility values for carers in the least **sever** state is a common method in appraisals of this disease area and was preferred by the committee in TA1031." | method in appraisals of this disease area and was preferred by the committee in TA1031." | |
| Incorrect labelling for health states 5 and 6<br><br>Page 14, Table 7 of the EAG addendum:<br><br>"5 **HTMF**, **night ventilation**"<br><br>"6 **No HTMF**, **no ventilation**" | "5 **No HTMF, no ventilation**"<br><br>"6 **HTMF, night ventilation**" | To correct a typographical error |
| Incorrect hazard ratio<br><br>Page 22, Table 10 of the EAG addendum: "Company's base-case + S1 + S3 + S4 + S5 + EAG's TE | "Company's base-case + S1 + S3 + S4 + S5 + EAG's TE Scenario 1: Applying the age at LOA **HR 0.469** (0.257, 0.855) with post-hoc selected | To correct a typographical error |

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| Scenario 1: Applying the age at LOA **HR 469** (0.257, 0.855) with post-hoc selected givinostat matched to CINRG DHNS) to transitions 1->2, 2->3 and 3->4 rather than just 2->3.” | givinostat matched to CINRG DHNS) to transitions 1->2, 2->3 and 3->4 rather than just 2->3.” | |