Single Technology Appraisal

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Santhera Pharmaceuticals:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Action Duchenne
   b. Duchenne UK (in collaboration with Action Duchenne and Muscular Dystrophy UK)
   c. Muscular Dystrophy UK
   d. Association of British Neurologists
   e. British Society for Paediatric Endocrinology & Diabetes and British Paediatric & Adolescent Bone Group

4. **Statements from experts**
   a. Robert Burley – patient expert, nominated by Muscular Dystrophy UK
   b. Mandy Roe – patient expert, nominated by Muscular Dystrophy UK
5. **External Assessment Report** prepared by Peninsula Technology Assessment Group

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

October 2023

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[ID40254]_vamorolone_Company_evidence_submission_Doc_B [ACIC]	**Final**	**Yes**	**4th Oct 23**

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Tables and figures

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

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication, that is, treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older. A summary of the decision problem is presented in Table 1.

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	Vamorolone for treating Duchenne muscular dystrophy.	Treatment of DMD in patients aged 4 years and older.	The population aged 4 to 7 years of age is supported by VISION-DMD and VBP15-LTE studies presented in B.2.3. Summary of methodology of the relevant clinical effectiveness evidence The population aged over 7 years of age is supported by an extrapolation report that includes Population Pharmacokinetics and Pharmacokinetics / Pharmacodynamics models as well as an ongoing Phase II Open-Label, Multiple Dose Study (VBP15-006) to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with DMD.
Intervention	Vamorolone.	Vamorolone.	Not applicable.

Comparator(s)	Established clinical management without vamorolone.	Established clinical management without vamorolone i.e., glucocorticoids, as per the clinical pathway of care presented in B.1.3. Health condition and position of the technology in the treatment pathway	Not applicable.
Outcomes	• Walking ability (ambulation) • Muscle function • Muscle strength • Ability to undertake activities of daily living • Bone function • Cardiac function • Concordance and optimisation of treatment • Endocrine function • Lung function • Time to wheelchair • Number of falls • Time to scoliosis • Upper body function • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Walking ability (ambulation) • Muscle function • Muscle strength • Bone function • Concordance and optimisation of treatment • Adverse effects of treatment • Health-related quality of life (for patients and carers)	Some outcomes were not recorded in the key studies of vamorolone. Both lung function and cardiac function are consequences of muscle function and time to wheelchair can be assessed through walking ability; both are presented as part of the study outcomes. A conservative estimate of equal mortality to steroids has been assumed within the model.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of	A cost-utility analysis was conducted in Excel using the Project HERCULES model framework.	Wider societal costs including productivity losses are important to capture as most DMD patients are cared for on a day-to-day, long-term

	incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Costs were considered from an NHS and PSS perspective. Direct health effects for patients and caregivers were considered. Wider societal costs including productivity losses to the patient and unpaid carers were also considered.	basis by a combination of formal caregivers (paid), family members and informal caregivers (i.e., non-professional, unpaid). Because the loss of function increases as DMD progresses, the care of DMD patients also increases over time with 24/7 care once patients are on full-time ventilation.

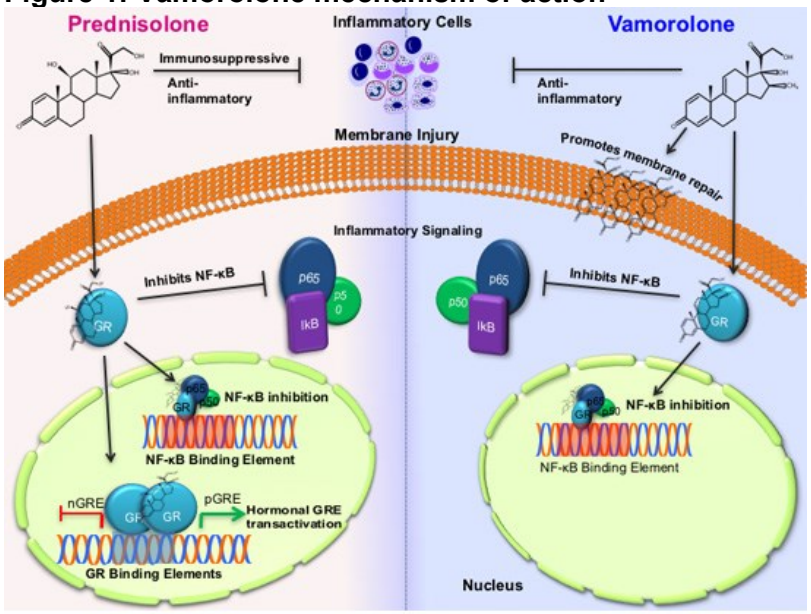
Abbreviations: DMD – Duchenne muscular dystrophy; LTE – Long-term extension; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PSS – Personal Social Services.

B.1.2. Description of the technology being appraised

A summary of vamorolone (Agamree®) is presented in Table 2. The draft Summary of Product Characteristics (SmPC) and United Kingdom (UK) public assessment report are presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Vamorolone (Agamree®).
Mechanism of action	The mechanism of action of vamorolone differs from traditional glucocorticoids by its lack of an 11β hydroxy-carbonyl group, which is a substrate for 11β-hydroxysteroid dehydrogenase (HSD) regulatory enzymes. Removal of this contact site with the glucocorticoid receptor alters structure and activity associations. This occurs through three documented pathways: 1. High affinity binding to the glucocorticoid receptor (NR3C1 gene), with potent suppression of NF-κB pro-inflammatory pathways.[1] 2. High affinity binding to the mineralocorticoid receptor (NR3C2 gene) with antagonist activity similar to eplerenone, potentially benefiting heart function.[1,2] 3. Membrane stabilisation and promotion of membrane repair in myofibers.[3] The predicted benefit to patients, as observed in two studies, include dose-responsive improvements in all gross motor function tests at 6 and 12 months of treatment, continued improvement in gross motor skills at 18 months of high dose treatment, and the declines in height velocity.[4,5] Importantly, initial reductions in BMC and BMD seen in prednisone treatment patients were reversed, demonstrating further support that vamorolone has a differential effect on bone health compared to prednisone.[6] The structural changes in the vamorolone steroidal backbone also leads to a predicted reduction in clinical safety concerns and side effects compared to corticosteroid use. This is demonstrated through biomarkers and clinical outcome assessments in open-label trials in both adult volunteers and DMD boys: 1. Reduced transcriptional activity via glucocorticoid response elements.[2] 2. Loss of impaired bone turnover and lack of growth stunting after 18 months of treatment.[7,8] 3. Less frequent cushingoid appearance.[4] 4. Small proportion of patients showing weight gain over 18 months of treatment.[4]

	5. Reduced vertebral facture rate.[9] As a consequence of these differences in structure, vamorolone preserves the anti-inflammatory activities associated with the efficacy of glucocorticoids, without the transactivation activities associated with adverse effects of this class of drugs. Treatment with glucocorticoids is part of the standard of care for both ambulatory and non-ambulatory patients with DMD, and replacement of glucocorticoids with vamorolone avoids several of the drug-induced adverse effects such as fractures, short stature, and osteopenia, while retaining or improving efficacy.[4] **Figure 1: Vamorolone mechanism of action**  *Abbreviations: GR – glucocorticoid receptor; GRE – glucocorticoid response element; nGRE – negative glucocorticoid response; pGRE – positive glucocorticoid response.* *Source: ReveraGen, 2023[10]*
Marketing authorisation/CE mark status	Within the EU, marketing authorisation is currently under review by the EMA with an expected approval in Q4 2023. Within the UK, an MAA submission to the MHRA will be made on receipt of a positive CHMP opinion through the EC Decision Reliance Procedure.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Vamorolone is indicated for the treatment of DMD in patients aged 4 years and older.
Method of administration and dosage	Treatment with vamorolone should only be initiated by specialised physicians with experience in the management of DMD. *4 years and older*

	The recommended dose of vamorolone is 6.0 mg/kg/day in patients weighing less than 40 kg. In patients weighing 40 kg and above, the recommended dose of vamorolone is 240 mg (equivalent to 6 ml) once daily. Daily dose may be reduced to 4 mg/kg/day, or 2 mg/kg/day based on individual tolerability. The dose of vamorolone must not be decreased abruptly if the treatment has been administered for more than one week. Dose reductions should be done progressively over weeks, by steps of approximately 20% decrease from the previous dose level. The duration of each reduction step should be adjusted depending on how patients react to the decreased dose.
Additional tests or investigations	No additional tests or investigations are required or anticipated.
List price and average cost of a course of treatment	The anticipated list price (excluding VAT) for 100ml of 40mg/ml of vamorolone is £4,585.87. The annual course of treatment based on the list price is: • £62,812 per year for 6mg/kg for a 25kg boy • £41,875 per year for 4mg/kg for a 25kg boy
Patient access scheme (if applicable)	A patient access scheme including a simple discount [redacted] has been proposed to NHS England.

Abbreviations: BMC – Bone mineral content; BMD – Bone mineral density; CHMP – Committee for Medicinal Products for Human Use; DMD – Duchenne muscular dystrophy; EC – European Commission; UK – United Kingdom; EMA – European Medicines Agency; EU – European Union; HSD - Hydroxysteroid dehydrogenase; Kg – Kilogram; MAA – Marketing Authorisation Application; mg – Milligram; MHRA – Medicines and Healthcare products Regulatory Agency; Ml – Millilitre; NHS – National Health Service; Q – Quarter; SmPC – Summary of Product Characteristics.
Source: Draft SmPC[11]

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

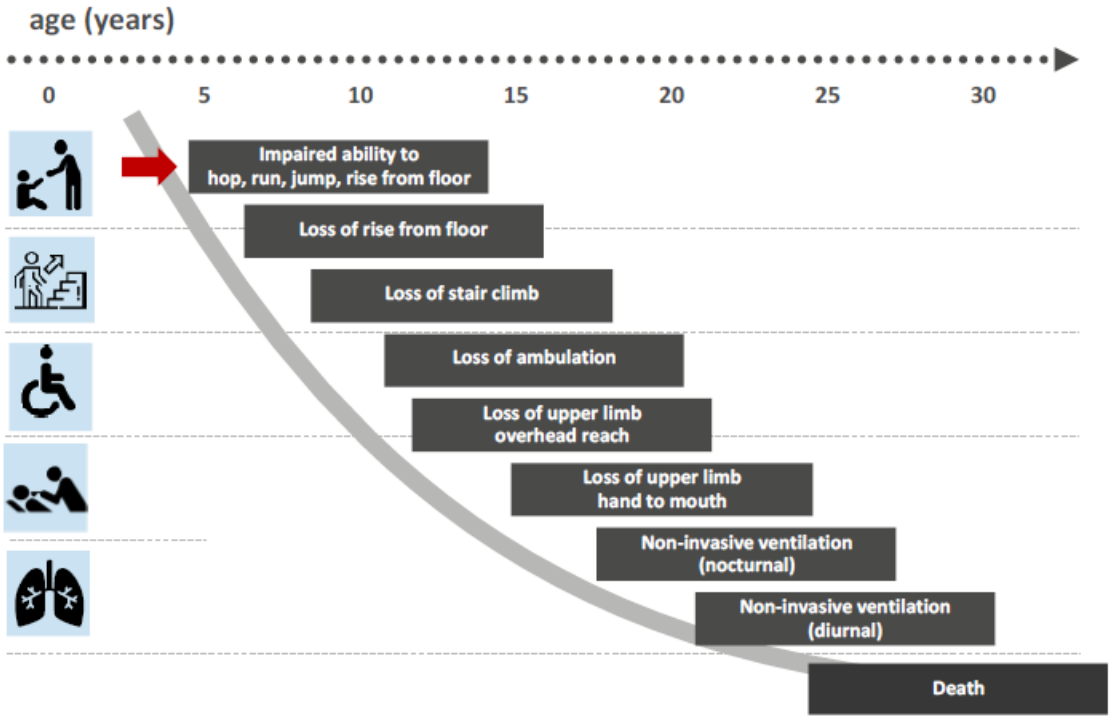
Disease background and epidemiology

DMD is one of the most common and severe forms of muscular dystrophy, characterised by debilitating muscle degeneration and weakness leading to progressive and severe long-term disability.[12,13] It is caused by mutations in the dystrophin gene located on the X chromosome that result in the loss of functional dystrophin, a protein present in the muscles which stabilises the cell membrane when the muscle contracts to prevent it from getting damaged by the contraction.

DMD is a genetic disorder, with age of onset usually between three and five years of age, although in some cases, symptoms can present in children as young as two years old.[14] Some early signs of DMD such as; large calf muscles (pseudohypertrophy), delayed independent sitting or standing, use of a Gower's movement to stand (walking hands up the legs to rise) and unusual gait when walking are likely to be present at diagnosis usually at three to five years.[15]

There is an almost exclusive prevalence of DMD in males. Boys begin to experience a decline in muscle strength in their hips and legs, leading to a loss of abilities such as running, climbing stairs, getting up from a lying position, and eventually, walking or bearing weight. As muscle strength decreases, weakness will spread to the arms and neck and over time, paralysis will set in, with the loss of arm and hand-function. Young adults can develop dysphagia, resulting in difficulty chewing and swallowing food and requiring a feeding tube. They will need help with all self-care activities, including; eating, drinking, toileting, dressing, washing, being moved into bed and being turned in bed. Respiratory function will also weaken as DMD progresses, leading to assisted ventilation, and the heart muscle will be affected, leading to cardiac failure.[15] Slowing the progression of DMD is therefore crucial to maximise patients' function, independence and quality of life (QoL). From the start of symptom presentation, DMD results in a rapid progression of muscle weakness and degeneration, as shown in Figure 2. Major stages in the disease are the loss of ambulation, the loss of self-feeding and the irreversible initiation of assisted ventilation.[13–16]

Figure 2: Typical muscle degeneration seen in patients with DMD



Abbreviations: DMD – Duchenne muscular dystrophy
Source: Data on file.

There is no curative treatment for this devasting disease. Mean life expectancy for DMD is less than 30 years due to respiratory and/or cardiac failure.[17–20] However, this is largely dependent on the rate of progression of muscular weakness and the impact on the patient's ambulatory and respiratory abilities. Furthermore, a diagnosis of DMD predicates a devastating impact on QoL for patients, families and caregivers, with gradually increasing physical impairment and dependency on other people until death.[21]

DMD is one of the most common forms of childhood muscular dystrophy, with a worldwide birth incidence of around 1 in 5,050 boys.[19] In the UK, approximately 100 boys are born each year with DMD, and it is thought that around 2,500 people will be living with the condition in the UK at any one time.[22] As this mutation occurs on the X chromosome, there is an almost exclusive prevalence of DMD in males since they only have one copy of the dystrophin gene. Female cases of DMD are extremely rare, around 1 case per 50 million births,[23] due to the existence of the additional X chromosome, which generally allows for sufficient dystrophin production.

Humanistic burden of disease

DMD is associated with significant disease-related burden for patients, families and caregivers in terms of physical, health demands, logistical, emotional, psychological, and financial burden.[24–34]

Given that symptoms can start presenting in children as young as two years old, from early childhood, DMD patients live their whole life with gradually increasing physical impairment and dependency on other people.[21] In the early stages, these symptoms include difficulty climbing stairs, walking and standing, resulting in frequent falls and considerably greater risks of fractures, causing greater physical burden and consequently demanding greater carer supervision. Physical impairment is particularly substantial in non-ambulant patients due to a general lack of strength and fatigue. As individuals lose ambulation, bones will become weaker, further increasing the risk of fractures.[35,36] Muscle weakness can hamper chewing and swallowing while cognitive impairment can lead to speech problems such as late onset of speaking, problems with word finding and difficulty in fluent language production.[34]

Patients can tire more easily due to the increased effort required to engage in daily activities, limiting their ability to participate freely with their peers.[32,34] This can result in psychological issues due to patients' increasing awareness of their disease and the impact this has on emotional wellbeing, leading to depression and anxiety. DMD patients experience above average rates of emotional and neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and obsessive compulsive disorder (OCD) which have considerable social and developmental implications if not sufficiently supported.[33] Some children also present with learning and behavioural difficulties, which have additional detrimental effects surrounding their social and academic capacities.

Most DMD patients are cared for on a day-to-day, long-term basis by a combination of informal caregivers (i.e., non- professional, paid or unpaid), family members and formal caregivers (paid). This includes emotional and social support and assistance with basic and instrumental activities of daily living (e.g., transfers to the wheelchair, preparing meals, cleaning, dressing, eating, and toileting).[24]

The physical burden of DMD is substantial once the patient is unable to mobilise unaided: for example, the lack of ambulation requires a mobility aid (scooter, specialist wheelchair to support the spine as muscles weaken) which needs to be accommodated in the home and at school, and has to be adapted over time to the child's growth.[24,37,38] Once wheelchair bound, patients experience a drastic decrease in independence, reduction in normal daily living and an increased risk of additional comorbidities. These comorbidities include the more rapid progression of muscular contractures and scoliosis. Scoliosis specifically leads to further orthopaedic issues, with the asymmetry between a patient's hip and shoulder having a detrimental impact on their chest cavity size and positioning, ultimately leading to respiratory issues requiring surgery. Independently, muscle weakening leads to impaired respiratory function, with increased need for cough and ventilatory support. Dystrophin deficiencies in the heart manifest as cardiomyopathy, which commonly presents in a patients' late teenage years (16 to 19 years old); between 70 and 90% of patients will develop it by the age of 20.[39] As the disease progresses, the myocardium fails to meet physiological demands and clinical heart failure develops. The failing myocardium is also at risk of life-threatening rhythm abnormalities.[40]

The burden, and therefore the impact on the carers, is further increased when patients have electrical wheelchairs, cough assist equipment, transfer lifts, hand-function assist devices and ventilators, not only because of the increased equipment but also the concern for electric/battery supply to ensure that, for example, the ventilator keeps working, both in the home and when out. The continuous loss of the upper limb function means that patients are not able to do their own cough assist nor to adapt the ventilator settings. The care of patients becomes 24/7 once patients are on full-time ventilation. As such, the need for round the clock medical care has a significant impact on the patient's ability to work and need for unpaid care over their lifetime. Without informal care, this level of care would otherwise be provided by paid professionals, the cost of which would be absorbed by the National Health Service (NHS) and Personal Social Services (PSS). Certain types of assisted ventilation, such as those with a mask, can have a significant impact on the ability to participate in daily activities, especially those outside of the home, as well as the ability to speak, further impairing patients' ability to communicate. It also prevents patients from kissing their loved ones.

Caring for DMD patients is time-consuming and has a severe negative impact on several aspects of daily living, including regular medical and related appointments requiring ongoing travel needs, home adjustments, parents' productivity, and bureaucracy requests to obtain reimbursement for various aspects of the child's care.[31,41]

Unsurprisingly, the mental health of carers is also impacted, with depression, stress, anxiety and feelings of isolation and exhaustion being prominent.[42,43] Mothers who are carriers of the dystrophin gene mutation that causes DMD often have elevated feelings of guilt, relating to the passing on of the disorder.[44] Parents often experience poor and frequently interrupted sleep due to needs such as changing bed position or checking ventilation. Additional factors including the financial strain of caregiving, physical exhaustion and lack of good quality professional respite care further impact carer QoL and also all incur greater losses in productivity.[45]

Landfeldt 2014 reported that caregivers who work had a mean loss in work time and productivity, corresponding to more than 1 day of a 5-day working week.[46]. Informal care and indirect costs together account for approximately 47% of total costs of illness in the UK.[46]

While parental burden is high in DMD, disease progression and an increase in burden means that even siblings are usually required to take care of the patient, which can lead to the onset of practical and psychological difficulties. These difficulties usually involve a negative impact on the social life of siblings (such as school performance and involvement in leisure activities) as well as a negative impact on their emotional wellbeing (such as being fearful, aggressive and shy).[47] Furthermore, some families may have two or more children with DMD due to the time of diagnosis of the older child, which leads to an even bigger burden on carers. Families and carers adapt as the disease progresses which could appear to affect some QoL results (e.g. reducing hours of work to a manageable amount).[48]

Health-related quality of life

Health-related quality of life (HRQL) in DMD can be viewed from the perspective of both the patient and the parents/carers. DMD is a progressive and unrelenting disease with increasing demands on the carer as the patient progresses to total dependency

on wheelchairs, loss of upper limb and hand-to-mouth function, assisted ventilation and increased need for support from carers.[49]

To accurately quantify the true detriment to patients' and carer's QoL, HRQL instruments should ideally capture multiple aspects of disease, such as mobility, psychosocial impact of disease, and other key physical parameters, such as the impact of the disease-related respiratory effects. Patient-reported outcomes (PRO) for DMD cannot capture the multi-dimensionality of the disease and all the changes that occur slowly over time. Patients born with degenerative diseases are acutely aware of the progressive nature of the disease and adapt to each change in their condition. However, for these patients, who have only ever experienced their disease from birth, there is no other state of health to compare to. Therefore, the benchmark for wellbeing or parameters measured by PROs are altered to account for this, resulting in positive scores for the PRO. Furthermore, approximately 30% of DMD patients have cognitive impairment and other disorders, such as ADHD, ASD and OCD. Given these complexities, using PRO scales to determine HRQL is challenging.[33,34,50,51] In particular, the EQ-5D is not a useful HRQL measurement tool in DMD patients as it lacks sensitivity, as discussed in Section Health-related quality of life data used in the cost-effectiveness analysis

Project HERCULES (Health Research Collaboration United in Leading Evidence Synthesis) is a unique UK-led project initiated by Duchenne UK to develop tools and evidence to support health technology assessment (HTA) and reimbursement decisions for new treatments in DMD. It brings together patients' groups, pharmaceutical companies, clinicians, academia, HTA agencies and other advisers to build a better evidence base for DMD. One of the initiatives of this multi-stakeholder collaboration was to review the appropriateness of current PRO scales for measuring QoL and, subsequently, to address these concerns through the development of a DMD-specific tool which is ongoing.[52,53]

There are currently no suitable HRQL questionnaires designed to fully capture the benefits of treatment. The Paediatric Quality of Life Inventory (PedsQL) is a generic tool that has been commonly used in DMD, however it has limitations; in particular, the DMD module does not capture small but clinically significant changes in the impact

of respiratory function decline.[52,54,55] In a recent review by Powell et al., it was noted that the development studies of the PedsQL were rated as doubtful and that there was little evidence to support the content validity of the neuromuscular module.[51]

Economic burden

The associated costs relating to patient comorbidities are substantial, and the accumulation of both direct and indirect costs impact the healthcare system, patients and carers. As the disease progresses, both the increased necessity for respiratory management and greater provision of medical aids (DMD patients requiring in-patient medical treatments from a median age of 14[56]) greatly contribute to the economic burden. Given the increased number of treatments and interventions required, DMD patients frequently experience adverse events (AEs) and recurrent hospitalisations which incur additional financial costs.

In the UK, the total annual per-patient cost of DMD was estimated around £59,000 (costs were presented in USD in the publication – and converted into Great British Pounds (GBP) for the submission - but are based on UK prices for the healthcare resource use data) based on an online questionnaire completed by 191 UK patient-caregiver pairs (including 44% non-ambulatory patients) identified via the Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) network.[46]

Direct annual per-patient costs, estimated at £44,000 (USD converted into GBP), represented 74% of the total annual cost. These costs comprised non-medical community services (e.g., home help, transportation services, nannies), informal care (carers' nonprofessional paid care and the proportion of carers' leisure time devoted to providing informal care), medical equipment, hospital admissions, tests, assessments and medication. Non-medical community service was the largest cost component (36% of the total direct cost), followed by informal care (26% of the total direct cost), while medication was the smallest cost component, representing under 2% of the total direct cost.[46]

Indirect annual per-patient costs associated with DMD were estimated at £15,000 (USD converted into GBP) due to the negative impact of the disease on patients' families, largely due to having to stop work in order to care for patients. Between 27%

and 49% of caregivers reduced their working hours or stopped working completely due to their son's DMD. The mean number of hours of leisure time devoted to informal caregiving per week was reported to be between 33 and 44 hours.[46] As the disease progresses, carer burden and time off work increases, emphasising the wider importance of slowing disease progression and reducing hospital appointments.[56]

Additional costs include those related to out of pocket expenses, including the cost of home alterations (including the addition of rails and ramps, door-widening to accommodate wheelchairs, bathroom and bedroom adjustments), the cost of transport to fit a wheelchair with all its equipment, the loss of leisure time and intangible costs related to the pain, anxiety and social handicap faced by patients and caregivers.[46]

Clinical pathway of care

There is no curative treatment for this devastating, progressive, neuromuscular disease with multi-system pathophysiology. Current treatment goals are aimed at delaying disease progression for as long as possible, and to anticipate and manage the associated complications, such as joint contractures, scoliosis, bone fractures, cardiomyopathy, respiratory insufficiency and treatment-related AEs.[57] A multidisciplinary approach is required to effectively manage patients, and includes neuromuscular management, rehabilitation interventions (such as physiotherapy, occupational therapy and speech language therapy), orthopaedic and surgical management, gastrointestinal and nutritional management, psychosocial, respiratory and cardiac management.[13,16]

Despite not being indicated for the treatment of DMD in the UK, glucocorticoids, including long-term prednisone or deflazacort dosing, are the current standard of care for DMD, as per the International DMD Care Considerations guidelines, and thus are the key comparators for this submission.[58] They are typically introduced between four to seven years old when muscle function decline becomes more pronounced. Glucocorticoids remain the mainstay of DMD treatment and continue after loss of ambulation.[13] While use of glucocorticoids has demonstrated significant benefits in minimising the progressive loss of muscular strength and consequently extending ambulatory function, avoiding scoliosis surgery, preserving upper limb function and

delaying the start of cardiac and respiratory function decline, they are associated with a number of severe side effects.[59]

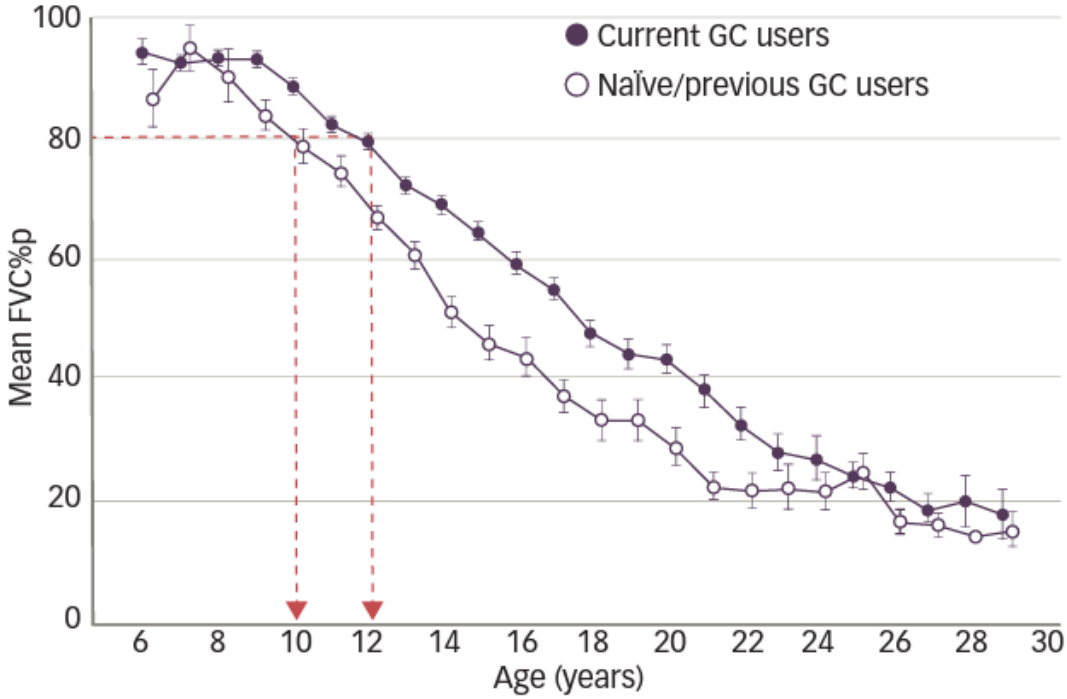
Such side effects include osteoporosis, reduced bone strength and increased risk of fractures, resulting from the potent osteotoxicity of glucocorticoid therapy combined with progressive myopathy.[16] This has an evident impact on patient mobility and independence, requiring additional reliance on others during recovery. Further AEs relating to bone health are also seen, with stunted growth a common side effect of glucocorticoid treatment as height velocity declines. In combination, these adverse bone and growth outcomes result in a shorter stature and negatively impact patient self-esteem and wellbeing, consequences both patients and carers have expressed concern over[60]. Glucocorticoids exacerbate the complex natural history of weight gain and weight maintenance in males with DMD, especially in non-ambulatory patients. Excess weight gain and obesity in adolescence is often followed by patients becoming underweight as they age.[61] Such weight gain is associated with obstructive sleep apnoea. Further side effects reported by DMD patients are severe mood swings and psychological effects, as well as cushingoid features, adrenal suppression, insulin resistance, cataracts and growth and development impediments.[62–64]

Whereas international guidelines do provide dosing guidance, no true consensus exists for the optimal dosing of glucocorticoids, and the choice for dosing regimen can be guided by the occurrence and severity of side effects.[4] The most frequently prescribed dose is 0.75 mg/kg/day, and there are regimens for daily and intermittent dosing.[65] Once the daily dose is not tolerated, there is no consensus on how to optimise. The severe side effects of glucocorticoids have been reported to impact effective dosing and discourages many patients and their carers to initiate or continue with treatment.[66] Side effects are reportedly responsible for around 65% of corticosteroid discontinuation, meaning these patients are not even receiving the benefits available with current treatment.[65]

Data from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS), showed that corticosteroid treatment shifts the onset of respiratory function loss by approximately two to three years when compared to patients not on corticosteroid therapy (as shown in Figure 3).[59] Time to

loss of ambulation and mobility was also extended in patients treated with glucocorticoids for a duration of over one year.[64]

Figure 3: Year-to-year drop in mean FVC%p over age classified by GC status



Abbreviations: FVC%p – forced vital capacity percent predicted; GC – glucocorticoid.
Data is mean (SEM). Red arrows indicate shift in start of pulmonary function decline by GC use of about two to three years.
Source: Mayer et al. 2017[59]

There is no curative treatment for DMD, and current standard of care suppresses height growth and delays puberty, suppresses normal bone transformation leading to osteoporosis with subsequent fractures, and does not stabilise and protect cell plasma membranes. As such, there is a significant unmet need for a licensed treatment that is equally as effective as existing therapies, but with a better tolerability that minimises the risks of damaging side effects associated with the current standard of care (i.e., glucocorticoids), encouraging greater uptake and continuation of treatment.

Vamorolone is anticipated to be offered to all patients with DMD aged four years and older to provide a well-tolerated, safe, and effective treatment without the damaging side effects seen with glucocorticoids, namely delayed puberty and growth and osteoporosis leading to bone fractures.

B.1.4. Equality considerations

No equality issues are foreseen with the use of vamorolone.

B.2. Clinical effectiveness

- Four key clinical studies of vamorolone have been conducted in DMD patients: the pivotal, randomised, double-blind, parallel-group, placebo- and active-controlled VISION-DMD study[4] provides key evidence; three Phase II studies provide supportive evidence.[8,67,68]
- In the VISION-DMD study, the primary clinical endpoint considered in the study was time to stand from supine (TTSTAND) velocity with vamorolone 6.0 mg/kg/day. Improvements were seen after just 6 weeks of treatment, compared to the slight decline seen in the placebo group.[4]
  - At Week 24,[4] the improvement in TTSTAND velocity was clinically meaningful, at almost twice the published minimally clinically important change, predictive of a delay of two to three years until loss of ambulation.[69]
- Additional secondary efficacy motor endpoints comprised the 6-minute walk test (6MWT), time to run/walk 10 metres (TTRW), time to climb four stairs (TTCLIMB) and the NorthStar Ambulatory Assessment (NSAA), with vamorolone demonstrating sustained improvements across all four.[4]
  - With the exception of TTRW, vamorolone elicited clinically meaningful differences across all other secondary endpoints. Importantly, after **48 weeks of treatment, the benefits established with vamorolone 6.0 mg/kg/day at Week 24 were sustained.**[5]
- Both vamorolone 6.0 and 2.0 mg/kg/day groups reported fewer clinically relevant AEs than prednisone, with no patients in either vamorolone group withdrawing from treatment.[4] **Crucially, following the switch from prednisone to vamorolone, annualised rates of AEs were reduced.**[5]
- **While height Z-score declined when treated with prednisone, after crossover to vamorolone, treatment reversal of growth trajectories was shown via catch-up growth.**[5] This was supported through a post-hoc, cross-study, indirect comparison that demonstrated height z-scores increased with vamorolone, in contrast to decreases seen with prednisone.[70]
- Patient bone health was maintained to a greater extent in vamorolone patients compared to prednisone, with significant reductions at Week 24 seen in all bone biomarkers in the prednisone group; **this was quickly reversed after crossover to vamorolone treatment.**[4,5]
- Overall, vamorolone is a safe, effective and well-tolerated treatment that has been shown to improve motor function. Vamorolone avoids several of the AEs associated with glucocorticoids, resulting in a favourable bone biomarker profile, no stunting of growth and fewer vertebral fractures (these fractures are predictive of future fractures).

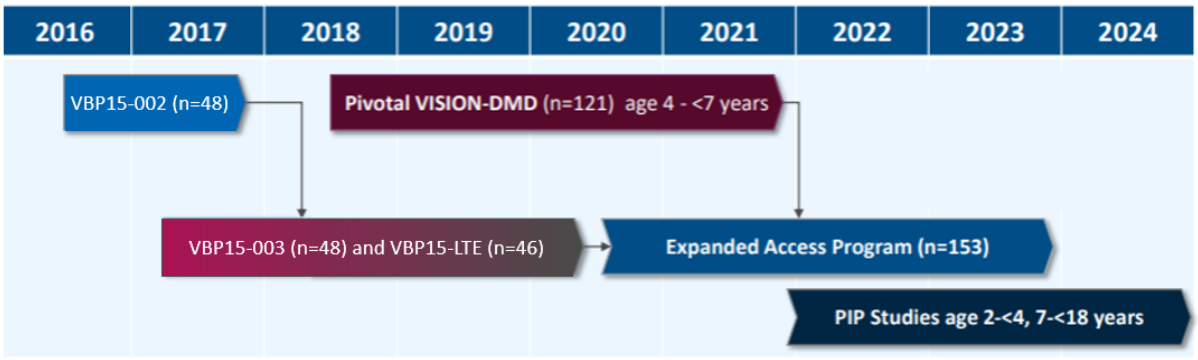
B.2.1. Identification and selection of relevant studies

See Appendix D for full details on the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2. List of relevant clinical effectiveness evidence

The clinical effectiveness of vamorolone in the treatment of DMD has been examined in a robust clinical trial program, as presented in Figure 4.

Figure 4: Overview of the vamorolone clinical trial program[71]



Abbreviations: LTE – Long-term extension; PIP – Paediatric investigational plan.

Study VBP15-002 (NCT02760264, Figure 4) was a Phase IIa, open-label, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and exploratory efficacy of vamorolone in boys with DMD, at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day for 2 weeks.[8,72] For detailed information on VBP15-002, see Table 4.

Study VBP15-003 (NCT02760277, Figure 4) was a Phase II, open-label, multicentre extension study to assess the long-term safety and efficacy of vamorolone in boys with DMD, administered at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day for six months to patients who completed Study VBP15-002.[67,73] For detailed information on VBP15-003, see Table 5.

In study VBP15-LTE (NCT03038399, Figure 4), a 24-month Phase II study, doses of up to 6.0 mg/kg/day were administered for an additional 24 months to patients who completed the 6-month VBP15-003 study (i.e. total treatment for 30 months or 2.5 years).[68,74] For VISION-DMD Phase 1 (24 weeks)detailed information on VBP15-LTE, see Table 6.

These three studies are summarised in Section B.2.3.3. VBP15-002, VBP15-003 and VBP15-LTE Results from VBP15-002 and VBP15-003 are presented in Appendix M, while results for VBP15-LTE are presented in B.2.6.3. VBP15-LTE

The pivotal trial, study VISION-DMD (NCT03439670), is a randomised double-blind, parallel-group, placebo- and active-controlled study to assess the efficacy and safety of vamorolone in ambulant boys with DMD.[4] The patients receiving vamorolone were treated with doses of 2.0 mg/kg/day and 6.0 mg/kg/day versus placebo and prednisone 0.75 mg/kg/day. This study is summarised in Table 3 and will be the focus of this section.

Table 3: Clinical effectiveness evidence, VISION-DMD[4]

Study	**VISION-DMD, NCT03439670.** **Primary publication for period 1: Guglieri et al.[4]** **Primary publication for period 2: Hoffman et al.[5]**	
Study design	Phase IIb, double-blind, randomised, placebo and active-controlled 48-week trial split into period 1, Week 1 to Week 24, a transition period of 4 weeks, and period 2, Week 29 to Week 48.	
Population	Ambulatory boys ages 4 to <7 years with DMD who were corticosteroid-naïve at study entry.	
Intervention(s)	Period 1 • Vamorolone 2.0 mg/kg/day. • Vamorolone 6.0 mg/kg/day.	Period 2 • Vamorolone 2.0 mg/kg/day. • Vamorolone 6.0 mg/kg/day.
Comparator(s)	Period 1 • Prednisone 0.75 mg/kg/day. • Placebo.	Period 2: None All patients who were previously treated with either prednisone or placebo were treated with vamorolone 2.0 or 6.0 mg/kg/day.
Indicate if study supports application for marketing authorisation	Yes.	
Indicate if study used in the economic model	Yes.	
Rationale if study not used in model	Not applicable.	
Reported outcomes specified in the decision problem	• TTSTAND • 6MWT • TTRW • TTCLIMB • NSAA score • Knee extension and elbow flexor muscle strength • HRQL, including the PODCI, the TSQM and the PARS III • Safety • Bone-related outcomes including P1NP, osteocalcin and CTX1	
All other reported outcomes	None.	

Abbreviations: 6MWT – 6-minute walk test; CTX1 – carboxy-terminal cross-linking telopeptide of type

I collagen; DMD – Duchenne muscular dystrophy; HRQL - Health-related quality of life; Kg – Kilogram; Mg – Milligram; NSAA – North Star Ambulatory Assessment; P1NP – serum procollagen type I N-terminal propeptide; PARS III – Psychosocial Adjustment and Role Skills Scale III; PODCI - Paediatric Outcomes Data Collection Instrument; TSQM – Treatment Satisfaction Questionnaire; TTCLIMB – time to climb 4 stairs; TTRW – time to run/walk 10m; TTSTAND – time to stand from supine.

Table 4: Clinical effectiveness evidence, VBP15-002

Study	**VBP15-002, NCT02760264.** **Primary publication: Conklin et al.[8]**
Study design	Phase IIa, open-label trial of vamorolone over 2weeks with sequential multiple ascending doses with a 2-week washout period (4 weeks).
Population	Boys aged 4 to <7 years with DMD.
Intervention(s)	• Vamorolone 0.25 mg/kg/day. • Vamorolone 0.75 mg/kg/day. • Vamorolone 2.0 mg/kg/day. • Vamorolone 6.0 mg/kg/day.
Comparator(s)	Not applicable.
Indicate if study supports application for marketing authorisation	No.
Indicate if study used in the economic model	No.
Rationale if study not used in model	VISION-DMD, VBP15-LTE and FOR-DMD provide sufficient clinical evidence to populate the economic model.
Reported outcomes specified in the decision problem	• Safety including AEs • Pharmacokinetics • Pharmacodynamics, including insulin resistance, low bone mineral density, and adrenal axis suppression
All other reported outcomes	None.

Abbreviations: AE – Adverse event; DMD – Duchenne muscular dystrophy; Kg – Kilogram; LTE – Long-term extension; Mg Milligram.

Table 5: Clinical effectiveness evidence – VBP15-003

Study	**VBP15-003, NCT02760277.** **Primary publication: Smith et al.[75]**
Study design	Phase II, open-label, multicentre 24-week study.
Population	Boys with DMD who had completed Study VBP15-002.
Intervention(s)	• Vamorolone 2.0 mg/kg/day. • Vamorolone 6.0 mg/kg/day. • Vamorolone 0.25 mg/kg/day. • Vamorolone 0.75 mg/kg/day.
Comparator(s)	Not applicable.
Indicate if study supports application for marketing authorisation	No.
Indicate if study used in the economic model	No.
Rationale if study not used in model	VISION-DMD, VBP15-LTE and FOR-DMD provide sufficient clinical evidence to populate the economic model.
Reported outcomes specified in the decision problem	• TTSTAND • 6MWT • TTRW • TTCLIMB • NSAA • Safety including AEs
All other reported outcomes	None.

Abbreviations: 6MWT – 6-minute walk test; AE – Adverse event; DMD – Duchenne muscular dystrophy; Kg – Kilogram; LTE – Long-term extension; Mg – Milligram; NSAA – North Star Ambulatory Assessment; TTCLIMB – Time to climb 4 stairs; TTRW – Time to run/walk 10m; TTSTAND – Time to stand from supine.

Table 6: Clinical effectiveness evidence, VBP15-LTE

Study	**VBP15-LTE, NCT03038399.** **Primary publication: Mah et al.[68]**
Study design	Phase II, non-randomised clinical trial over a 24-month time period.
Population	Boys with DMD who had completed VBP15-003.
Intervention(s)	• Vamorolone 0.25 mg/kg/day. • Vamorolone 0.75 mg/kg/day. • Vamorolone 2.0 mg/kg/day. • Vamorolone 6.0 mg/kg/day. Multiple dose escalations to the highest dose (6.0 mg/kg/day) were permitted.
Comparator(s)	Not applicable.
Indicate if study supports application for marketing authorisation	Yes.
Indicate if study used in the economic model	Yes.
Rationale if study not used in model	Not applicable.
Reported outcomes specified in the decision problem	• TTSTAND • 6MWT • TTRW • TTCLIMB • NSAA • QMT • HRQL, through the PODCI • Safety
All other reported outcomes	None.

Abbreviations: 6MWT – 6-minute walk test; DMD – Duchenne muscular dystrophy; HRQL – Health-related Quality of life; Kg – Kilogram; Mg – Milligram; NSAA – North Star Ambulatory Assessment; PODCI – Paediatric Outcomes Data Collection Instrument; QMT - Quantitative Muscle Testing; TTCLIMB – Time to climb 4 stairs; TTRW – Time to run/walk 10m; TTSTAND – Time to stand from supine.

FOR-DMD (NCT03038399) is a Phase III, double-blind, randomised clinical trial comparing prednisone 0.75 mg/kg/day, deflazacort 0.90 mg/kg/day and intermittent prednisone 0.75 mg/kg/day (10 days on, 10 days off) in corticosteroid-naïve boys aged 4 to <7 years with DMD.[76] A matched comparison of VISION-DMD and FOR-DMD was conducted to compare vamorolone to prednisone and deflazacort at 48 weeks, as per discussions with the European Medicines Agency (EMA). This is presented in Section B.2.9. Indirect and mixed treatment comparisons Full details of FOR-DMD are available in Table 7.

Table 7: Clinical effectiveness evidence – FOR-DMD

Study	**FOR-DMD, NCT01603407.** **Primary publication: Guglieri et al.[76]**
Study design	Double-blind, parallel-group randomised clinical trial.
Population	Boys aged 4 to 7 with DMD who were glucocorticoid treatment naïve.
Intervention(s)	• Prednisone 0.75 mg/kg/day. • Prednisone 0.75 mg/kg/day (10 days on, 10 days off). • Deflazacort 0.9 mg/kg/day.
Comparator(s)	N/A.
Indicate if study supports application for marketing authorisation	Yes.
Indicate if study used in the economic model	Yes.
Rationale if study not used in model	N/A.
Reported outcomes specified in the decision problem	• TTSTAND • 6MWT • TTRW • NSAA • HRQL, including TSQM • Safety including AEs
All other reported outcomes	• TTRF • BMI • FVC • Ankle range of motion • Cardiac function

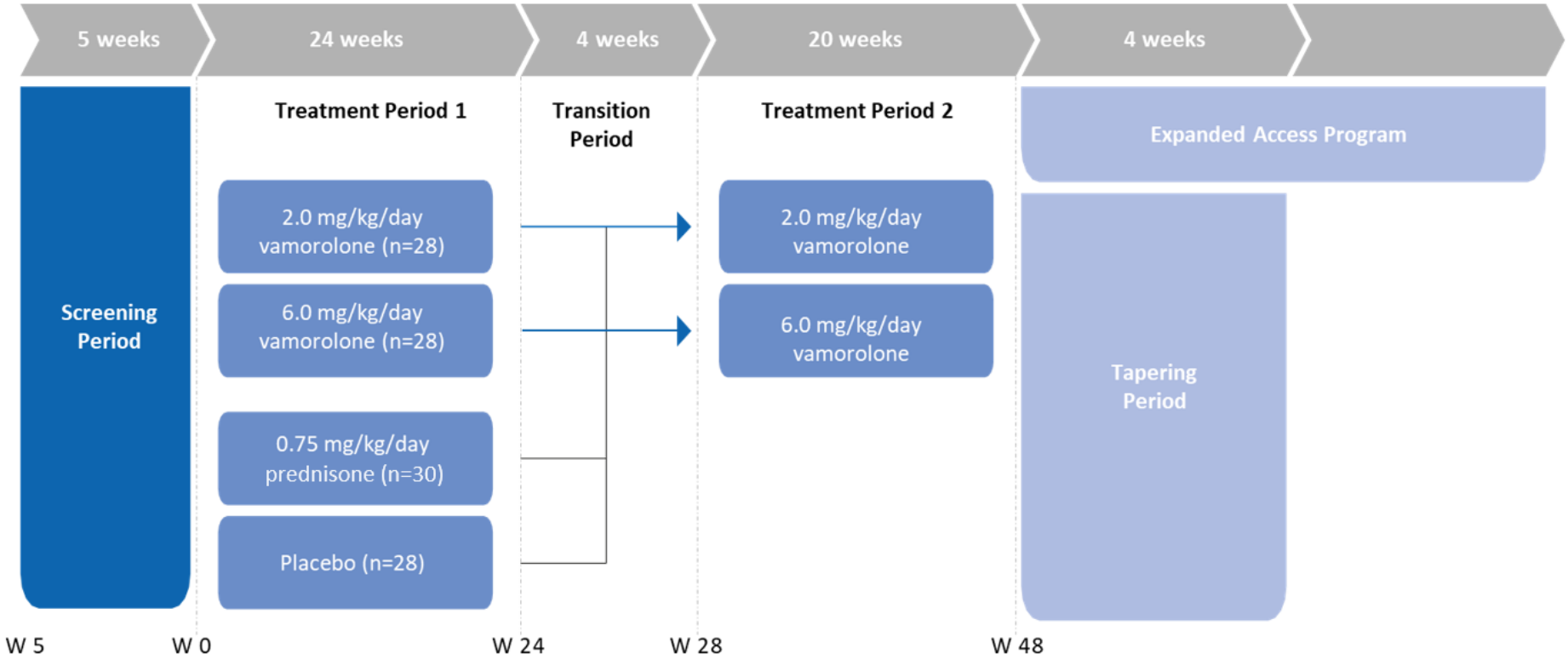
Abbreviations: 6MWT – 6-minute walk test; AE – Adverse event; BMI – Body mass index; DMD – Duchenne muscular dystrophy; FVC – Forced vital capacity; HRQL – Health-related quality of life; Kg – Kilogram; Mg – Milligram; NSAA – North Star Ambulatory Assessment; TSQM – Treatment Satisfaction Questionnaire;; TTRF – Time to rise from floor; TTRW – Time to run/walk 10m; TTSTAND – Time to stand from supine.

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

B.2.3.1. Summary of trial methodology

VISION-DMD is a Phase IIb randomised, double-blind, parallel-group study, conducted in collaboration with the CINRG, to evaluate the efficacy, safety, PD and PK of vamorolone in ambulatory boys with DMD who were corticosteroid-naïve at study entry. As detailed in Section B.2.3.2. Patient demographics and baseline characteristics this study was conducted at 33 qualified study centres, including six in the UK.[6] The study design is shown in Figure 5.

Figure 5: Study design of VISION-DMD[71]



Abbreviations: Kg – Kilogram; Mg – Milligram; W – week.

The study consisted of a screening period from Day -33 to Day -2, followed by a 24-week randomised period (period 1) to determine if vamorolone treatment led to improvements in strength and mobility compared with placebo treatment and to compare the AE profile for vamorolone with the AE profiles for placebo and prednisone.[4] In period 1, patients were randomised in a 1:1:1:1 ratio to 1 of 4 groups: placebo, vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, or prednisone 0.75 mg/kg/day. Randomisation was stratified by age at study entry (<6 years and ≥6 years) and was conducted using an Interactive Voice/Web Response System (IXRS). To maintain the double-blind nature in this treatment period, all patients received either a matching placebo for vamorolone (i.e., a placebo oral suspension), a matching placebo for prednisone (i.e., a placebo tablet) or both (i.e., placebo oral suspension and placebo tablet).

Following completion of period 1, all patients entered a 4-week transition period (i.e., Week 25 to Week 28) during which vamorolone or its matching placebo were administered at the same dose as in treatment period 1, but the dose of prednisone and its matching placebo tablet were tapered to zero.[4]

Patients entered period 2 (Week 29 to Week 48) after completion of the transition period. In treatment period 2, all patients who were previously treated with either prednisone or placebo were randomised to vamorolone 2.0 or 6.0 mg/kg/day; patients who had received vamorolone in treatment period 1 were continued on the same vamorolone dose in this treatment period (Table 8).[5]

Table 8: Randomisation schedule for treatment periods

Group	Period 1 (Week 1 – Week 24)	Period 2 (Week 29 – Week 48)
1	Vamorolone 2.0 mg/kg/day.	Vamorolone 2.0 mg/kg/day.
2	Vamorolone 6.0 mg/kg/day.	Vamorolone 6.0 mg/kg/day.
3	Prednisone 0.75 mg/kg/day.	Vamorolone 2.0 mg/kg/day.
4	Prednisone 0.75 mg/kg/day.	Vamorolone 6.0 mg/kg/day.
5	Placebo.	Vamorolone 2.0 mg/kg/day.
6	Placebo.	Vamorolone 6.0 mg/kg/day.

Abbreviations: Kg – Kilogram; Mg – Milligram.
Source: Hoffman et al. 2023[5]

Following completion of period 2, patients were offered the opportunity to continue vamorolone in either an Expanded Access Program (EAP) (if enrolled in Canada, Israel, or the United States) or other special access program. Special access programs enable drugs that are not marketed in a patient's country of residence to be requested

by practitioners for the treatment, diagnosis, or prevention of serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. In the UK, vamorolone is provided under Named Patient Based Access, which is the supply of unauthorised medicines for individual patients in response to requests by doctors on behalf of specific patients. This access is limited to the requested named patient or patients only. Patients could alternatively transition to the standard of care for DMD. The EAP allows patients access to vamorolone alongside standard of care treatment for DMD. Patients who elected to transition to standard of care entered a 4-week dose-tapering period in which the dose of vamorolone was progressively reduced and discontinued.

The primary endpoint was change from baseline to Week 24 in TTSTAND velocity for the vamorolone 6.0 mg/kg/day group compared with placebo.[4] TTSTAND is a linear measurement expressed as the number of seconds taken to rise from a supine position without assistance. The TTSTAND declines rapidly over time in patients with DMD and has been previously shown to be an early prognostic factor for disease progression and loss of ambulation.[77,78] TTSTAND velocity is a conversion of TTSTAND. It is calculated as 1/TTSTAND, expressed as rises per second. It is designed to overcome the limitations of TTSTAND for patients with long rise times or who can no longer rise without assistance that are inputted as zero, and the better statistical properties reduce the impact of outliers. A velocity of at least 0.2 rises per second is a minimal clinically important difference (MCID), associated with increased probability of losing standing ability, and a change in velocity of 0.05 rises per second is considered to be a MCID.[79]

Secondary efficacy motor endpoints included the 6MWT, TTRW, TTCLIMB and the NSAA total score for both the 6.0 mg/kg/day group and the 2.0 mg/kg/day group.[4] 6MWT assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity/endurance and TTCLMIB is often used in DMD studies.[80] The NSAA is a 17-item rating scale that is used to measure functional motor abilities in ambulant children with DMD. It is usually used to monitor the progression of the disease and treatment effects. It uses a scale of 0 (unable), 1 (completed independently but with modifications), and 2 (completed without compensation). The timed 10-metre run/walk and timed rise from floor are conducted as part of the NSAA. The higher the total

score, the more mobile the patient is. Repeat NSAA tests performed over time can be used to compare changes in physical disease progression.[81]

Strength outcomes were handheld myometry of elbow flexor muscles and knee extensor muscles.[4] Motor assessments were done by trained clinical evaluators at screening, baseline, 12 weeks, and 24 weeks. Parent-reported outcomes were Paediatric Outcomes Data Collection Instrument (PODCI), Psychosocial Adjustment and Role Skills Scale III (PARS III), and Treatment Satisfaction Questionnaire (TSQM).

Safety endpoints (clinical and laboratory) were assessed at screening, baseline, and Weeks 2, 6, 12, 18, and 24.[4] A standard-dose corticotropin (ACTH) stimulation test measuring cortisol at baseline and 30 and 60 minutes after tetracosactide 250 µg, diagnostic testing was done at screening and Week 24.

A summary of the methodology of VISION-DMD is shown in Table 9.

Table 9: Summary of VISION-DMD methodology

Trial design	**Phase 2b randomised, double-blind, parallel-group study**
	Randomisation: 1:1:1:1 by Interactive Voice and web response system (IXRS) after patients were confirmed to have met all study entry criteria, at least 10 days prior to the Baseline Day -1 Visit). **Stratification factors:** Age at study entry (<6 years and ≥6 years). **Blinding:** This was a double-blind study in which the investigator, study site staff, patient's parent/legal guardian, patient, and study monitors were unaware of the treatment assignment throughout the duration of the study. To maintain the study blind, matching placebos for vamorolone and prednisone were used. The investigator was allowed to break the study blind only if he/she felt the patient's clinical circumstance required knowledge of the treatment assignment. Selected sponsor and data analysis personnel were unblinded after data lock for period 1 to enable analyses of Week 24 treatment data according to SAP. All clinical study staff, including the investigator, study site staff, and non-statistical study management staff remained blinded until after data lock for period 2.
Duration of study	First patient enrolled: 29 June 2018. Last Patient Completed: 19 August 2021. Duration of treatment: 48 weeks.
Settings and locations where data were collected	The study was conducted at 33 qualified study centres in Australia (2 centres), Belgium (2 centres), Canada (4 centres), the Czech Republic (2 centres), Greece (1 centre), Israel (1 centre), The Netherlands (2 centres), Spain (2 centres), Sweden (1 site), United Kingdom (6 centres), and US (10 centres).
Participant eligibility criteria	**Key inclusion criteria** • Parent(s) or legal guardian(s) provided written informed consent and Health Insurance Portability and Accountability Act authorisation, where applicable, prior to any study related procedures; participants were asked to give written or verbal assent according to local requirements.

	• Had a centrally confirmed diagnosis of DMD (by a genetic counsellor with Therapeutic Research in Neuromuscular Disorders Solutions) defined as any one of the following: o Dystrophin immunofluorescence and/or immunoblot showing complete dystrophin deficiency with a clinical picture consistent with typical DMD. o Identifiable mutation within the DMD gene (deletion/duplication of one or more exons), where reading frame was predicted as "out-of-frame" with a clinical picture consistent with typical DMD. o Complete dystrophin gene sequencing showed an alteration (point mutation, duplication, or other) that precluded production of the dystrophin protein (i.e., nonsense mutation, deletion/duplication leading to a downstream stop codon), with a clinical picture consistent with typical DMD 3. • Was ≥4 years and <7 years of age at time of enrolment in the study. • Weighed >13.0 kg and ≤39.9 kg at Screening. • Was able to walk independently without assistive devices. • Was able to complete the TTSTAND without assistance in <10 seconds at Screening. • Clinical laboratory tests within normal range at Screening or were not clinically significant if abnormal in the opinion of the investigator. Note: Serum GGT, creatinine, and total bilirubin all must have been ≤ULN range at Screening. An abnormal clinically significant vitamin D level did not exclude a patient from randomisation. • Had evidence of chicken pox immunity as determined by any one of the following: o Presence of IgG antibodies to varicella documented by a positive test. From the local laboratory from blood collected during the screening period. o Documentation provided at Screening that the patient had two doses of varicella vaccine, with or without serologic evidence of immunity; the second of the two immunisations must have been administered at least 14 days before randomisation. • Was able to swallow tablets, confirmed by successful test swallowing of placebo tablets during the screening period. • Patient and parent(s)/guardian(s) were willing and able to comply with scheduled visits, study drug administration plan, and study procedures.
	Key exclusion criteria • Had major renal or hepatic impairment, diabetes mellitus, or immunosuppression or a history of any of these conditions. • Had a chronic systemic fungal or viral infection or a history of these infections. • Had an acute illness within 4 weeks prior to the first dose of study medication. • Had used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), mexrenone (mexrenoate potassium) within 4 weeks prior to the first dose of study medication. • Had a history of primary hyperaldosteronism. • Had evidence of symptomatic cardiomyopathy. Note: an asymptomatic cardiac abnormality was not exclusionary. • Was currently being treated or had received previous treatment with oral glucocorticoids or other immunosuppressive agents. Note: Past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months prior to first dose of study medication, was considered for eligibility on a case by-case basis, unless discontinued for intolerance. Inhaled and/or topical glucocorticoids were permitted if last use was at least 4 weeks prior to first

	dose of study medication or if administered at a stable dose beginning at least 4 weeks prior to first dose of study medication and anticipated to be used at this dose regimen for the duration of the study. • Had an allergy or hypersensitivity to either study medication or any of its constituents. • Had used idebenone within 4 weeks prior to the first dose of study medication. • Had severe behavioural or cognitive problems that precluded participation in the study in the investigator's opinion. • Had a previous or ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up would be correctly completed or impair the assessment of study results in the opinion of the investigator. • Was taking (or had taken within 4 weeks prior to the first dose of study medication) herbal remedies and supplements which could impact muscle strength and function (e.g., co-enzyme Q10, creatine, etc). • Was taking (or had taken within 3 months prior to the first dose of study medication) any medication indicated for DMD, including Exondys51 and Translarna. • Had received a live attenuated vaccine within 14 days prior to the first dose of study medication. • Was currently taking any other investigational drug or had taken any other investigational drug within 3 months prior to the first dose of study medication. • Had a sibling who was currently enrolled in any study or EAP for vamorolone or who intended to enrol in any study or EAP during the patient's participation in the VISION-DMD study. • Had previously been enrolled in the study.
Trial drugs	**Intervention:** Vamorolone was administered orally at daily doses of 2.0 mg/kg/day and 6.0 mg/kg/day. Patients in the vamorolone 2.0 mg/kg/day were administered a vamorolone 1.33% wt/wt oral suspension and patients in the vamorolone 6.0 mg/kg/day group were administered a vamorolone 4.0% wt/wt oral suspension. **Comparator:** Either prednisone 0.75 mg/kg/day or its matching placebo were administered orally as tablet(s) based on weight bands once daily.
	Patients who elected to not continue vamorolone treatment following completion of treatment period 2 entered a 4-week dose-tapering period in which the vamorolone dose was tapered to zero.
Concomitant medication	**Permitted concomitant medication:** Use of either inhaled and/or topical glucocorticoids was permitted, provided that the dose was stable beginning at least 4 weeks before the first dose of study drug and was anticipated to be stable for the duration of the study. Patients with past transient use of oral or inhaled glucocorticoids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months (or last use at least 1 month prior for inhaled glucocorticoids) before the first dose of study drug were eligible for the study on a case-by-case basis. Hydrocortisone (or prednisone) stress dosing was permitted during an illness, injury, or surgical procedure to avoid an adrenal crisis. **Prohibited concomitant medication:** The following medications were not permitted before the first dose of study drug and were prohibited for the duration of the study: • Mineralocorticoid receptor agents (ie, spironolactone, eplerenone, canrenone [canrenoate potassium], prorenone [prorenoate potassium], mexrenone [mexrenoate potassium] were discontinued at least 4 weeks prior to the first dose of study drug. • Oral glucocorticoids or other oral immunosuppressive agents, with the exceptions noted above.

	• Idebenone at least 4 weeks prior to first dose of study drug. • Medications indicated for the treatment of DMD, including Exondys51 and Translarna, at least 3 months prior to first dose of study drug. • Any approved medications or herbal remedies that could impact strength and function (including, but not limited to, Co-enzyme Q10, creatine) at least 4 weeks before the first dose of study drug. • Any investigational medications other than vamorolone at least 3 months before the first dose of study drug.
Primary endpoint	Change from baseline to Week 24 in TTSTAND velocity for vamorolone 6.0 mg/kg/day compared with placebo.
Secondary endpoints	Secondary efficacy endpoints for Week 24 listed in order of pre-specified hierarchical statistical testing, included the following: • Change from baseline in TTSTAND velocity for vamorolone 2.0 mg/kg/day compared with placebo. • Change from baseline in 6MWT distance for vamorolone 6.0 mg/kg/day compared to placebo. • Change from baseline in 6MWT distance for vamorolone 2.0 mg/kg/day compared to placebo. • Change from baseline in TTRW distance for vamorolone 6.0 mg/kg/day compared to placebo. • Change from baseline in TTRW distance for vamorolone 2.0 mg/kg/day compared to placebo. • Change from baseline in 6MWT distance for vamorolone 6.0 mg/kg/day compared to prednisone. • Change from baseline in 6MWT distance for vamorolone 2.0 mg/kg/day compared to prednisone. Additional secondary endpoints for Week 24 were not tested for multiple comparisons and included the following comparing each of the vamorolone doses versus placebo and each vamorolone dose versus prednisone: • Change from baseline in TTCLIMB velocity. • Change from baseline in NSAA score. • Change from baseline in knee extension muscle strength. • Change from baseline in elbow extension muscle strength.
Exploratory endpoints	• Range of motion of the ankle joint. • Treatment satisfaction using the TSQM. • Physical functioning using the PODCI. • Creatine kinase.

Safety endpoints	• AEs, SAEs and AESIs.
	• Bone health assessments, including:
	  ○ BMD by DXA scan.
	  ○ Lateral spinal x-rays.
	  ○ Bone formation markers, (P1NP) and osteocalcin.
	  ○ Bone reabsorption marker, serum CTX1.
	  ○ Fracture questionnaire.

Pre-planned subgroups	Analyses of TTSTAND velocity for vamorolone 6.0 mg/kg/day vs placebo were conducted for the following subgroups: • Age: patients ≤5 years vs >5 years at baseline (cut-off by expected median age). • Age: patients ≤6 years vs >6 years at baseline (cut-off for stratification at randomisation). • Baseline TTSTAND velocity: patients with TTSTAND ≤5.0 seconds vs >5.0 seconds at baseline. • Baseline TTSTAND velocity: subset of patients with TTSTAND between ≥4 to ≤7 seconds at baseline (to rule out the possible impact of very short or very long rise times).

	• Baseline 6MWT distance: subset of patients excluding those with a missing 6MWT baseline value. • Baseline 6MWT distance <350 metres. • Race: patients of Caucasian race versus other races conducted only if <90% of patients were Caucasian). • Country: patients enrolled in US (including Canada/Australia) vs Europe (including Israel).

Abbreviations: 6MWT – 6-minute walk test; AE – Adverse event; AESI – Adverse events of special interest; BMD – Bone mineral density; CTX1 – Carboxy-terminal cross-linking telopeptide of type I collagen; DMD – Duchenne muscular dystrophy; DXA - Dual-energy X-ray absorptiometry; EAP – Expanded Access Program; GGT – Gamma-glutamyl transferase; IgG – Immunoglobulin G; IXRS - Interactive voice and web response system; Kg – Kilogram; Mg – Milligram; NSAA – North Star Ambulatory Assessment; P1NP – Serum procollagen type I N-terminal propeptide; PARS III – Psychosocial Adjustment and Role Skills Scale III; PODCI – Paediatric Outcomes Data Collection Instrument; SAE – Serious adverse-event; SAP – Statistical analysis plan; TSQM – Treatment Satisfaction Questionnaire; TTCLIMB – Time to climb 4 stairs; TTRW – Time to run/walk 10m; TTSTAND – Time to stand from supine; ULN – Upper limit of normal; US – United States.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

B.2.3.2. Patient demographics and baseline characteristics

Of the 133 patients screened for the study, 121 patients were randomised at 33 sites, including six UK sites: 30 patients each in the vamorolone 6.0 mg/kg/day, vamorolone 2.0 mg/kg/day, and placebo groups and 31 patients in the prednisone group.[4]

Most patients were either White or Asian and not Hispanic or Latino (Table 10). Mean age was approximately 5 years in all of the groups (range: 4 to <7 years).[4] Height was lower in the vamorolone 6.0 mg/kg/day group compared with the other groups whereas weight and body mass index (BMI) were lower in the vamorolone and placebo groups compared with the prednisone group (Table 10). Patients in the vamorolone groups had slower TTSTAND velocity, shortened 6MWT distance, and lower NSAA scores at baseline (Table 10).

Table 10: Patient demographics in VISION-DMD (mITT Population)

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)	Total (n=118)
Age (years)*, mean (SD)	5.38 (0.83)	5.54 (0.86)	5.32 (0.91)	5.42 (0.88)	5.41 (0.86)
Weight (kg), mean (SD)	20 (3)	21 (3)	19 (4)	19 (3)	20 (3)
BMI Z-score	0.53 (0.79)	0.87 (0.77)	0.44 (0.89)	0.67 (0.82)	0.63 (0.82)
Height (cm), mean (SD)	109 (9)	111 (6)	108 (9)	107 (7)	109 (8)
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)	Total (n=118)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	16.3 (1.1)	16.8 (1.3)	16.2 (1.2)	16.6 (1.4)	16.5 (1.3)
TTSTAND velocity (rises/sec), mean (SD)	0.20 (0.07)	0.22 (0.06)	0.18 (0.06)	0.19 (0.06)	0.20 (0.06)
6MWT distance (metres), mean (SD)	357.12 (77.07)	343.32 (55.84)	316.07 (58.43)	312.50 (56.19)	332.39 (63.85)
NSAA total score	18.97 (5.22)	21.16 (5.45)	17.20 (4.67)	18.86 (4.07)	19.07 (5.04)
TTRW velocity (m/s), mean (SD)	1.7 (0.3)	1.9 (0.4)	1.6 (0.3)	1.6 (0.4)	1.7 (0.4)

* 'Age (years)' are relative to patient's informed consent date.
Abbreviations: 6MWT – 6-minute walk test; BMI – Body mass index; Kg – Kilogram; Mg – Milligram; mITT – modified Intent-to-Treat; NSAA – North Star Ambulatory Assessment; SD – Standard deviation; TTRW – Time to run/walk 10m; TTSTAND – Time to stand from supine.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

B.2.3.3. VBP15-002, VBP15-003 and VBP15-LTE

In addition to the pivotal VISION-DMD study, vamorolone was assessed in three Phase II studies in boys with DMD.[8,67,68]

VBP15-002 was a Phase IIa open-label, multiple ascending dose study to assess the safety, tolerability, PK, PD, and exploratory efficacy of vamorolone in steroid-naïve boys aged 4 to <7 years with DMD.[8] A total of 48 patients enrolled and completed this study with 12 patients assigned to each of the four dose cohorts: 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day for 2 weeks with a 2-week washout period (4 weeks). A summary of the results of VBP15-002 are provided in Appendix M.

Patients enrolled in Study VBP15-002 were enrolled in VBP15-003, a Phase II open-label, multicentre 24-week extension study to assess the long-term safety and efficacy of vamorolone in boys with DMD.[67] Vamorolone doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day were administered for 6 months. Dosing was followed by consumption of a 240 mL glass of full-fat milk or fat equivalent because vamorolone absorption is increased by high-fat food. The study enrolled 48 steroid-naïve ambulant boys aged 4 to <7 years with DMD, with 12 boys in each of the same dose cohorts. A summary of the results of VBP15-003 are provided in Appendix M.

The key objective in VBP15-003 was to assess if there was a dose response relationship of orally administered vamorolone to improvement of gross motor strength

and endurance through a dose-escalation study design, and to assess the extent to which vamorolone has the pharmacodynamic safety concerns of glucocorticoids. Other endpoints included TTSTAND, TTRW, 6MWT, TTCLIMB, NSAA and safety assessments.

Data from vamorolone-treated DMD boys in the VBP15-003 study were compared to steroid-naïve DMD patients of the same age group (4 to <7 years) from the CINRG DNHS. While the CINRG DNHS is an external comparator for the vamorolone trial, the two studies use similar recruitment sites, clinical evaluators, clinical evaluator training, and outcome measures.

Following completion of VBP15-003, 46 patients continued in the extension study VBP15-LTE.[68] Patients were assigned to receive vamorolone at one of four dose levels (0.25, 0.75, 2.0 or 6.0 mg/kg/day) and were then either escalated to a dose between 2.0 and 6.0 mg/kg/day or maintained between 2.0 and 6.0 mg/kg/day. A total of 23 patients maintained between 2.0 and 6.0 mg/kg/day until the end of follow-up while 23 patients up-titrated to a dose between 2.0 and 6.0 mg/kg/day until the end of follow-up.[68] Dose de-escalations were allowed in case of intolerability. Patients from the CINRG DNHS treated with glucocorticoids were selected to serve as a historical control group for timed function tests and patients from the NorthStar UK (NSUK) Network were chose to serve as a second historical control group for comparison of NSAA scores since NSAA was not assessed for most patients in DNHS. The primary objective of this long-term extension was to assess the efficacy, safety and tolerability of vamorolone among boys with DMD who completed the 6-month dose-finding and 24-month long-term extension trials, with a total of up to 30 months vamorolone treatment. Secondary objectives were to indirectly compare outcomes with the CINRG DNHS cohort treatment with glucocorticoids (n=75; mean age 6.08 years) and participants of the NSUK Network as a second historical control to compare NSAA scores (n=110; mean age 6.0 years).

Efficacy analyses in this study included TTSTAND, TTRW, TTCLIMB, 6MWT, NSAA score and quantitative muscle testing using the CINRG Quantitative Measurement System. PROs were assessed using the PODCI, which consists of 83 questions and

five subscale scores with scores ranging from 0-100 where lower scores indicate lower HRQL. Safety and AE reporting was also assessed.

A summary of the methodology of VBP15-LTE is shown in Table 11.

Table 11: Summary of VBP15-LTE methodology

Trial design	**Non-randomised controlled open-label extension** This was an open-label study, and therefore no randomisation or blinding was applicable.
Duration of study	24 months.
Settings and locations where data were collected	11 US and non-US study sites.
Participant eligibility criteria	Inclusion criteria: • Subject's parent or legal guardian has provided written informed consent and HIPAA authorisation (if applicable) prior to any VBP15-LTE-specific procedures. • Subject has previously completed study VBP15-003 up to and including the Week 24 Final assessments, prior to enrolling in the VBP15-LTE study at the conclusion of the VBP15-003 Week 24 Visit [Note: if entering the dose-tapering period, subject is enrolling within 8 weeks after the VBP15-003 final visit following dose-tapering]. • Subject and parent/guardian are willing and able to comply with scheduled visits, study drug administration plan, and study procedures. Exclusion criteria: • Subject had a serious or severe adverse event in study VBP15-003 that, in the opinion of the Investigator, was probably or definitely related to vamorolone use and precludes safe use of vamorolone for the subject in this long-term extension study. • Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression. • Subject has current or history of chronic systemic fungal or viral infections. • Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), mexrenone (mexrenoate potassium) within 4 weeks prior to the first dose of study medication. • Subject has evidence of symptomatic cardiomyopathy. (Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary). • Subject is currently being treated or has received previous treatment with oral glucocorticoids or other immunosuppressive agents (Notes: Past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 3 months cumulative, with last use at least 3 months prior to first dose of study medication, will be considered for eligibility on a case-by-case basis. Inhaled and/or topical glucocorticoids prescribed for an indication other than DMD are permitted but must be administered at stable dose for at least 3 months prior to study drug administration). • Subject has used idebenone within 4 weeks prior to the first dose of study medication. • Subject has an allergy or hypersensitivity to the study medication or to any of its constituents.

	• Subject has severe behavioural or cognitive problems that preclude participation in the study, in the opinion of the Investigator. • Subject has previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up will be correctly completed or impair the assessment of study results, in the opinion of the Investigator. • Subject is currently taking any investigational drug or has taken any investigational drug other than vamorolone within 3 months prior to the start of study treatment.
Trial drugs	**Intervention:** Vamorolone was administered orally at daily doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day. Patients were administered a vamorolone 4.0% wt/wt oral suspension. Subjects received vamorolone throughout the 24-month treatment period, initially at the same dose level they received at the time they completed the final visit of the VBP15-003 Phase IIa extension study. Patients were eligible to be escalated to the next higher-dose level at the discretion of the Study Chair and Medical Monitor, after they were on their initial dose for at least 1 month.
Concomitant medication	**Permitted concomitant medication:** Use of either inhaled and/or topical glucocorticoids was permitted, provided that the dose was stable beginning at least 4 weeks before the first dose of study drug and was anticipated to be stable for the duration of the study. Patients with past transient use of oral or inhaled glucocorticoids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months (or last use at least 1 month prior for inhaled glucocorticoids) before the first dose of study drug were eligible for the study on a case-by-case basis. Hydrocortisone (or prednisone) stress dosing was permitted during an illness, injury, or surgical procedure to avoid an adrenal crisis. **Prohibited concomitant medication:** The following medications were not permitted before the first dose of study drug and were prohibited for the duration of the study: • Mineralocorticoid receptor agents (i.e., spironolactone, eplerenone, canrenone [canrenoate potassium], prorenone [prorenoate potassium], mexrenone [mexrenoate potassium] were discontinued at least 4 weeks prior to the first dose of study drug. • Oral glucocorticoids or other oral immunosuppressive agents, with the exceptions noted above. • Idebenone at least 4 weeks prior to first dose of study drug. • Medications indicated for the treatment of DMD, including Exondys51 and Translarna, at least 3 months prior to first dose of study drug. • Any approved medications or herbal remedies that could impact strength and function (including, but not limited to, Co-enzyme Q10, creatine) at least 4 weeks before the first dose of study drug. Any investigational medications other than vamorolone at least 3 months before the first dose of study drug.
Primary endpoint	TTSTAND velocity (rise/second): Comparison with a historical natural history (untreated) control group for change from Baseline to Month 24.
Secondary endpoints	• TTSTAND velocity (rise/second): Comparison with a historical natural history (untreated) control group for change from Baseline to Month 12. • TTSTAND: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • 6MWT: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • TTRW: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • TTCLIMB: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points.

	• NSAA: Change in timed assessments and total score from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • QMT: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points.
Exploratory endpoints	• PODCI: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points. • Levels of additional exploratory PD biomarkers. • DNA testing for established genetic modifiers of DMD.
Safety endpoints	• BMI Z-score: Comparison with prednisone- and deflazacort-treated historical control groups for change from Baseline to Month 12 and Month 24. • BMI Z-score: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • Height Z-score: Comparison with prednisone- and deflazacort-treated historical control groups for change from Baseline to Month 12 and Month 24. • TEAEs and SAEs by SoC: Overall by treatment, by treatment and relationship, and by treatment and intensity. • Vital signs [blood pressure, heart rate, respiratory rate, oral body temperature]: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • Body weight: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • Clinical laboratory values (haematology and biochemistry): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • Lipid profile (triglycerides, total cholesterol, LDL, HDL): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • Urinalysis by dipstick and microscopic analysis: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • 12-lead ECG: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points. • Hand x-ray: bone age at Month 24. • Spine x-ray: Spine fractures at Month 24.
Pre-planned subgroups	None planned.

Abbreviations: 6MWT – 6-minute walk test; BMI – Body mass index; DMD – Duchenne muscular dystrophy; DNA - Deoxyribonucleic acid; ECG – Electrocardiogram; HDL – High density lipoprotein; HIPAA – Health Insurance Portability and Accountability Act; LDL – Low density lipoprotein; Kg – Kilogram; LTE – Long-term extension; Mg – Milligram; NSAA – North Star Ambulatory Assessment; PD – Pharmacodynamics; PODCI – Paediatric Outcomes Data Collection Instrument; QMT – Quantitative muscle testing; SAE – Serious adverse event; SoC – System organ class; TEAE – Treatment-emergent adverse event; TTCLIMB – Time to climb 4 stairs; TTRW – Time to run/walk 10m; TTSTAND – Time to stand from supine; US – United States.
Source: Mah et al. 2022[68]

B.2.3.4. Patient demographics and baseline characteristics

Among 46 boys with DMD who completed the dose-finding study, 41 participants (89.1%; baseline mean [SD] age, 5.33 [0.96] years) completed the 2-year LTE treatment period. Five participants withdrew for reasons unrelated to the study drug. At the month 24 visit, 11 participants, three participants, and 27 participants were

being treated at 2.0 mg/kg/day, 4.0 mg/kg/day, and 6.0 mg/kg/day, respectively. Analysis of treatment efficacy focused on 23 participants receiving 2.0 or 6.0 mg/kg/day vamorolone who were initially assigned and maintained on 2.0 mg/kg/day or more for up to 30 months during the dose-finding study (6 months) and LTE study (24 months). Demographic and clinical characteristics of participants in the LTE study receiving higher doses are summarised in Table 12. The mean (SD) baseline age was 5.83 (0.88) years in the group receiving 2.0 or 6.0 mg/kg/day vamorolone (higher-dose). In the higher-dose LTE group, 3 participants (13.0%) withdrew before the LTE month 24 study visit.

Table 12: Patient demographics in VBP15-LTE[a]

	Vamorolone 2.0 or 6.0 mg/kg/day (n=23)[b]	GC in CINRG DNHS (n=75)	GC in NSUK (n=110)[c]
Age (years)*, mean (SD)	5.83 (0.88)	6.08 (0.81)	6.00 (0.77)
Weight (kg), mean (SD)	21.98 (3.78)	20.35 (3.55)	NA
BMI, mean (SD)	17.68 (1.23)	16.68 (1.55)	NA
Height (cm), mean (SD)	111.80 (6.94)	10.9.86 (6.86)	NA
Steroid exposure at baseline comparison visit (days), mean (SD)	200.57 (7.54)	227.73 (61.91)	264.84 (57.39)
Duration of follow-up from baseline visit (years[d]), mean (SD)	1.85 (0.46)	1.36 (0.49)	NA
Participants with >18-month follow-up after initial 6 months of steroid exposure, n (%)	21 (91.3)	30 (40.0)	NA

[a] Based on baseline comparator visit, which corresponds to approximately 6 months of steroid exposure for participants in the NSUK Network and CINRG DNHS.
[b] Refers to patients assigned to vamorolone 2.0 or 6.0 mg/kg/day from initial dose-finding studies and maintained at 2.0 mg/kg/day or more from VBP15-LTE baseline.
[c] Owing to NSUK Network participant-level data-sharing restrictions, limited summary of information was available.
[d] Reported for TTSTAND.
Abbreviations: CINRG – Cooperative International Neuromuscular Research Group; DNHS – Duchenne Natural History Study; GC – glucocorticoid; Kg – Kilogram; NA – Not applicable; NSUK – NorthStar UK; SD – Standard deviation
Source: Mah et al. 2022[68]

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

B.2.4.1. Analysis sets

The analysis sets included in the VISION-DMD study are presented in in Table 13. As the study had two treatment periods, there were two modified Intent-to-Treat (mITT) analysis sets and two safety analysis sets.

Table 13: VISION-DMD Analysis sets

Analysis sets	
Screened	All patients who provided informed consent, including screen failures.
Intent-to-Treat	All randomised patients.
mITT 1	All randomised patients who had at least one dose of study medication and had at least one post-baseline efficacy assessment* during period 1; this was the primary analysis population for efficacy at Week 24.
mITT 2	All randomised patients who had at least one dose of study medication and had at least one post-baseline efficacy assessment* during period 2; this was the primary analysis population for efficacy at Week 48.
Per Protocol	Patients in the mITT population with no major protocol deviations**; this was a secondary analysis population for efficacy at Week 24.
Safety-1	All patients who received at least one dose of study medication during period 1; this was the analysis population for safety at Week 24.
Safety-2	All patients who completed period 1 and received at least one dose of vamorolone during period 2; this was the analysis population for safety at Week 48.

* A post-baseline efficacy assessment was defined as at least one non-missing assessment of TTSTAND, TTRW, TTCLIMB, 6MWT, NSAA, myometry, or range of motion.
** Major protocol deviations were identified by patient before Week 24 analysis
Abbreviations: mITT – modified Intent-to-Treat.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

B.2.4.2. Statistical analyses

Statistical methods used in VISION-DMD are summarised below (Table 14).

Table 14: VISION-DMD summary of statistical analyses

Hypothesis objective	The null hypothesis was that there was no difference in the change from baseline in TTSTAND velocity at Week 24 between vamorolone 6.0 mg/kg/day and placebo.
Sample size, power calculation	Sample sizes were determined based on published prednisone treatment efficacy from a CINRG prednisone trial in the same age range and then re-analysed from analysis of vamorolone open-label trial data. The sample size of 30 per treatment group for 2.0 mg/kg/day, 6.0 mg/kg/day, prednisone, and placebo (i.e., total enrolment of 120 patients) provided approximately 91% power at alpha level 0.05 to detect a statistically significant difference between 6.0 mg/kg/day and placebo on TTSTAND velocity at Week 24.
Statistical analyses	**Primary efficacy endpoint: TTSTAND velocity** The primary efficacy endpoint was the change from baseline to Week 24 in TTSTAND velocity for the vamorolone 6.0 mg/kg/day group vs the placebo group. TTSTAND velocity was calculated as 1/TTSTAND expressed as rises per second. The primary analysis methods for TTSTAND recommended by FDA and EMA were different, with FDA requesting an analysis using observed data only (i.e., without imputation) and EMA requesting a multiple imputation method for missing data. *FDA analysis* The primary analysis of TTSTAND for FDA was conducted with a restricted maximum likelihood (REML)-based MMRM using observed cases (without multiple imputation) and the mITT-1 analysis set. The MMRM included TTSTAND velocity values (as changes from baseline) from Weeks 6, 12, and 24 as dependent values. The model included fixed effects for baseline age (as stratified at randomisation), group (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo), week

	(Week 6, 12, or 24), and treatment-by- week interaction. Baseline TTSTAND velocity was included as a covariate. Within this model, pairwise comparisons (using least squares mean [LSM] contrasts) of TTSTAND velocity at Week 24 were made for vamorolone 6.0mg/kg/day with placebo. An unstructured covariance structure was applied for MMRM. If this analysis fails to converge, Akaike's information criterion will be used to select the best covariance structure from compound symmetry and autoregressive-1 (AR(1)). The denominator degrees of freedom will be computed using the Kenward-Roger method. *EMA analysis* The primary analysis for EMA was conducted using multiple imputation, with analysis consisting of the following steps: 1. Imputation of all intermittent missing data with multiple imputation assuming MAR to generate a dataset with a monotone missing data structure. 2. Based on the dataset generated in Step 1: imputation of all monotone missing data with multiple imputation assuming MAR to generate a dataset with no missing data. 3. Based on dataset generated in Step 2 (with no missing data): all visits with monotone missing data that were not due to COVID-19 were set back as missing. 4. Based on dataset generated in Step 3: imputation of remaining monotone missing data (not related to COVID-19) with multiple imputation assuming MNAR (Copy-Reference imputation. 5. Based on dataset generated in Step 4, analysis of imputed data with MMRMs. 6. Combination of results from the MMRMs. **Secondary efficacy endpoints: vamorolone vs placebo** TTSTAND velocity was calculated as described above. TTRW velocity was calculated as 10/TTRW expressed as metres per second and TTCLIMB velocity was calculated as 1/TTCLIMB expressed as tasks per second. The NSAA score was the sum of all NSAA 17-item scores, with the score set as missing if any one of the item scores was missing. Elbow flexor and knee extensor strength were each summarised using the best of the three results at each visit. No further derivation was done, and missing assessments were left as missing. The secondary efficacy endpoint TTSTAND velocity (vamorolone 2.0 mg/kg/day vs placebo) was analysed as described for FDA and EMA above. The other secondary efficacy endpoints, including the 6MWT distance, TTRW velocity, TTCLIMB velocity, NSAA score, and knee extension and elbow extension muscle strength, were also analysed as described for FDA and EMA above, comparing vamorolone 6.0 mg/kg/day vs placebo and vamorolone 2.0 mg/kg/day vs placebo. **Secondary efficacy endpoints: vamorolone vs prednisone at Week 24** TTSTAND velocity, 6MWT distance, TTRW velocity, TTCLIMB velocity, NSAA score, and knee and elbow extension muscle strength were compared for each vamorolone dose vs prednisone at Week 24 using an MMRM model, observed cases (i.e., without multiple imputation) and the mITT-1 analysis set. The MMRM included the response values (as changes from baseline) from Weeks 6, 12, and 24 as dependent values. The model includes fixed effects for baseline age (as stratified in randomisation), group (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, or prednisone 0.75 mg/kg/day), week (Week 6, 12, or 24) and treatment-by-week interaction. The baseline response value was included as a covariate. Within this model, pairwise comparisons (using LSM

contrasts) were made to compare the treatment difference between vamorolone 6.0 mg/kg/day or 2.0 mg/kg/day with prednisone. An unstructured covariance structure was applied for MMRM. If this analysis fails to converge, Akaike's information criterion was used to select the best covariance structure from compound symmetry and autoregressive-1 (AR(1)). The denominator degrees of freedom were computed using the Kenward-Roger method.

Formal statistical testing of 6MWT distance for vamorolone 6.0 mg/kg/day followed by 2.0 mg/kg/day vs prednisone was only conducted if the pre-specified hierarchical testing order specified above held (i.e., p values ≤0.05).

For TTSTAND velocity, 6MWT distance, TTRW velocity and NSAA score, the comparison of efficacy endpoints between the vamorolone groups and prednisone group were focused on a global assessment of efficacy, aiming to show that the efficacy profile of the two vamorolone doses was comparable to prednisone. There was no predefined order of the endpoints and for each endpoint, the treatment differences and 95% CIs calculated with MMRM were summarised.

Exploratory endpoints

Exploratory efficacy endpoints included the following:

- Range of motion of the ankle joint.
- Treatment satisfaction using the TSQM.
- Physical functioning using the PODCI.

Range of motion for the left and right ankle joint was summarised descriptively.

Treatment satisfaction scores for each of the four subscales of the TSQM were summarised as follows:

- Global Satisfaction: ([Sum (Item 10 to Item 11) – 2] divided by 12) x 100
  - If one item was missing: ([(Use the completed item)) – 1] divided by 6) x 100.
- Effectiveness: ([(Item 1 + Item 2) – 2] divided by 12) x 100.
  - If one item was missing: ([(Use the completed item)) – 1] divided by 6) x 100.
- Side Effects: ([Sum (Item 4 to Item 6) – 3] divided by 12) x 100.
  - All "not applicable" responses were coded as '5' indicating "not at all dissatisfied".
  - If one item was missing: ([(Sum (the two completed items)) – 2] divided by 8) x 100.
- Convenience: ([Sum(Item 7 to Item 9) – 3] divided by 18) x 100.
  - If one item was missing: ([(Sum (the two completed items)) – 2] divided by 12) x 100.

The Upper Extremity and Physical Function score of the PODCI was calculated as [(4 - mean of non-missing questions used to calculate the raw score)/3] x 100. Response scores of five indicated that the patient was too young for the activity and were set to missing when calculating the subscale score.

The Transfers and Basic Mobility score of the PODCI was calculated as [(4 - mean of non-missing questions used to calculate the raw score)/3] x 100. Responses to the last two questions (How often does your child need help from another person for sitting and standing? How often does your child use assistive devices (such as braces, crutches, or wheelchair) for sitting

	and standing?) were rescaled if used in calculating the sum and standardise score as follows: rescaled = [(response - 1) x 3/4] + 1. Response scores of five indicated that the patient was too young for the activity and were set to missing when calculating the subscale score. **Safety analyses** Safety analyses were conducted using the SAF-1 and SAF-2 analysis sets. No formal statistical hypothesis testing was performed for the safety endpoints.
Data management, patient withdrawals	Partial or missing dates for concomitant medications and AEs were inputted (if necessary). The handling of missing data for the EMA analysis has been described above. If the TTSTAND test could not be performed, the reason for not being able to perform the test was utilised in definition of the endpoint as follows: • Velocity was set as zero for responses determined to be missing due to disease progression (as documented on the eCRF). • At the first visit a patient could not perform the TTSTAND test because of disease progression and at all subsequent visits conducted without performing the TTSTAND test, the raw score was left as missing, and velocity was set as 0. • However, a patient could not have a missing response due to disease progression followed by visits with responses. In this scenario, the missing response was not considered missing due to disease progression and was left as missing. • If the patient discontinued the study, the velocity values were set as missing for the visits that were not conducted. If the patient died during the study, the velocity was set as zero at the visit following the death and considered as missing at subsequent visits. The pattern of missing TTSTAND data over time and the cause of missing TTSTAND data were summarised by visit. For each visit, data were classified as available or missing, with missing data classified as follows: • Intermittent (missing value was followed by an observed value). • Measurement dropouts (all subsequent values after the missing value were missing). The number and percentage of patients in each of the above categories were summarised by visit. Additionally, the reasons for missing data were classified as due to the COVID-19 pandemic, disease-related disability, or other reasons. A diary to record missed or incomplete doses of study medication and new concomitant medications or changes to existing concomitant medications was maintained by the patient's parent/legal guardian throughout the study.
Interim analyses	No interim analysis was planned or conducted for this study.

Abbreviations: 6MWT – 6-Minute Walk Test; AE – Adverse-event; CI – Confidence interval; CINRG – Cooperative International Neuromuscular Research Group; eCRF - Electronic case report form; EMA – European Medicines Agency; FDA – Food and Drug Administration Kg – Kilogram; LSM – Least squares mean; MAR – Missing at random; Mg – Milligram; mITT – Modified Intent-to-treat; MMRM – Mixed model for repeated measures; MNAR – Missing not at random; NSAA – North Star Ambulatory Assessment; PODCI – Paediatric Outcomes Data Collection Instrument; REML – Restricted maximum likelihood; SAF-1 – Safety Analysis Set 1; SAF-2 – Safety Analysis Set 2; TSQM – Treatment Satisfaction Questionnaire; TTCLIMB – Time to climb 4 stairs; TTSTAND – Time to stand from supine; TTRW – Time to run/walk 10m.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

B.2.4.3. Minimal clinically important difference

The MCID is the smallest difference in outcome measure that would be noticeable to a patient and be of clinical relevance.

A retrospective analysis of prospectively collected data from a multicentre natural history study with the CINRG was performed. This study calculated the minimal detectable change (MDC) and MCID values for three commonly used timed function tests typically used to monitor disease progression: supine to stand (STS); 10-minute walk test (10MWT); 4 stair climb (4SC). These three measures were deemed to be significantly important clinical endpoints to detect MDC and MCID changes. MDC and MCID 12-month changes were significant in 10MWT (–0.138, –0.212), STS (–0.026, –0.023) and 4SC (–0.034, –0.035) with an effect size greater than or close to 0.2.[69]

Using the data from a study by McDonald et al., and the study by Duong et al., a clinical trial that compared two doses of vamorolone with placebo and prednisone in boys with DMD aged 4 to younger than 7 years of age and glucocorticoid-naïve, observed that the differences in TTSTAND velocity (0.06 rises per second for vamorolone 6.0 mg/kg/day versus placebo and 0.05 rises per second for vamorolone 2.0 mg/kg/day versus placebo) were clinically meaningful (>0.02 rises per second).[69,80] The differences in 6MWT (42 m for vamorolone 6.0 mg/kg/day versus placebo and 37 m for vamorolone 2.0 mg/kg/day versus placebo) were also clinically meaningful (>30 m).[4]

A team of researchers conducted a study reviewing the MCID for the NSAA on behalf of the iMDEX Consortium and the UK NorthStar Clinical Network. The boys with DMD included in this study ranged in age from 6.5 years to 10.5 years, of which 94.5% were (or had been) treated with glucocorticoids. A descriptive questionnaire was used to capture patient and parent perspectives on the changes in NSAA scores, which they regarded as meaningful. Depending on whether the standard deviation (SD) or the standard error of measurement (SEM) was used, the MCID for NSAA in this cohort ranged from 2.3–2.9 points (SD), or 2.9–3.5 points (SEM).[82]

In the clinical trials for vamorolone, the MCID for various outcomes were defined as shown in Table 15, based on several studies, and in comparison to placebo. The MCID was consistent across each of the studies.

Table 15: Minimal clinically important different (MCID) thresholds in clinical trials

Rank	Endpoint	Comparison vs placebo	Difference	MCID	P-value
Primary	TTSTAND velocity	Vamorolone 6.0 mg/kg/day	0.06 rises/sec	>0.023 rises/sec	0.002
Pre-specified, hierarchical secondary	TTSTAND velocity	Vamorolone 2.0 mg/kg/day	0.04 rises/sec	>0.023 rises/sec	0.017
	6MWT	Vamorolone 6.0 mg/kg/day	42 metres	>26-32 metres	0.003
	6MWT	Vamorolone 2.0 mg/kg/day	37 metres	>26-32 metres	0.009
	TTRW velocity	Vamorolone 6.0 mg/kg/day	0.24 m/sec	>0.212 m/sec	0.002
	TTRW velocity	Vamorolone 2.0 mg/kg/day	0.13 m/sec	>0.212 m/sec	0.103
Exploratory	TTCLIMB velocity	Vamorolone 6.0 mg/kg/day	0.07 task/sec	>0.035 task/sec	<0.001
	TTCLIMB velocity	Vamorolone 2.0 mg/kg/day	0.06 task/sec	>0.035 task/sec	<0.006
	NSAA	Vamorolone 6.0 mg/kg/day	3.4 points	>2.32 points	<0.001
	NSAA	Vamorolone 2.0 mg/kg/day	3.2 points	>2.32 points	<0.001

Abbreviations: 6MWT – 6-minute walk test; Kg – Kilogram; MCID – Minimal clinically important difference; Mg – Milligram; NSAA – North Star Ambulatory Assessment; TTCLIMB – Time to climb 4 steps; TTRW – Time to run/walk 10 metres; TTSTAND – Time to stand from supine.
Source: Duong et al.[69], Guglieri et al.[4], Ayyar Gupta et al.[82]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of VISION-DMD was conducted using the National Institute for Health and Care Excellence (NICE) single technology assessment user guide, adapted from the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care; results are shown in Table 16.[83] Overall VISION-DMD was deemed to be a high quality study with minimal risk of bias.

Table 16: VISION-DMD quality assessment results

Questions	VISION-DMD
Was randomisation carried out appropriately?	**Yes:** Patients were randomised 1:1:1:1 ratio by an IXRS after patients were confirmed to have met all study entry criteria, at least 10 days prior to the Baseline Day -1 Visit). Patients were stratified by age at study entry (<6 years and ≥6 years).
Was the concealment of treatment allocation adequate?	**Yes.** To maintain the double-blind in this period 1, all patients received either a matching placebo for vamorolone (i.e., a placebo oral suspension), a matching placebo for prednisone (i.e., a placebo tablet) or both (i.e., placebo oral suspension and placebo tablet). Maintenance of the blind was aided by use of amber bottles and acceptability for taste for both the vamorolone and placebo suspensions.
Were the groups similar at the outset of the study in terms	**Yes:** There was no significant difference in the baseline characteristics reported between the treatment arms.

Questions	VISION-DMD
of prognostic factors?	
Were the care providers, participants and outcome assessors blind to treatment allocation?	**Yes:** Investigators, study site staff, patient's parent/legal guardian, patient, and study monitors were unaware of the treatment assignment throughout the duration of the study.
Were there any unexpected imbalances in dropouts between groups?	**No:** There were no unexpected imbalances in dropouts between groups. Withdrawals by patients were similar in all arms up to Week 24 (prednisone, n=1; placebo, n=2; vamorolone 2.0 mg/kg/day, n=2; vamorolone 6.0 mg/kg/day, n=2) and up to Week 48 (prednisone, n=1; placebo, n=2; vamorolone 2.0 mg/kg/day, n=2; vamorolone 6.0 mg/kg/day, n=4).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No:** No evidence to suggest that the authors measured more outcomes than they reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes:** Efficacy analysis was performed using the mITT-1 population for efficacy at Week 24 and using the mITT-2 population for efficacy at Week 48. Following the Intent-to-Treat principle, patients were analysed according to the treatments and strata to which they were assigned at randomisation. For missing data: The FDA requested an analysis using observed data only (i.e., without imputation) and EMA requested a multiple imputation method for missing data.

Abbreviations: EMA – European Medicines Agency; FDA – Food and Drug Administration; IXRS – Interactive voice and web response system; Kg – Kilogram; Mg – Milligram; mITT – Modified Intent-to-Treat.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

B.2.6. Clinical effectiveness results of the relevant studies

B.2.6.1. Week 24 results, VISION-DMD

B.2.6.1.1. Primary efficacy endpoint: TTSTAND velocity with vamorolone 6.0 mg/kg/day

As presented in Table 17 and Figure 6, vamorolone 6.0 mg/kg/day significantly improved TTSTAND velocity compared to placebo, with a least square mean (LSM) change from baseline of 0.05 (standard error [SE]: 0.01) rises per second compared with -0.01 (SE: 0.01) respectively (LSM difference: 0.06 rises per second [95% CI: 0.02-0.10]; p=0.002).[4]

The improvement in TTSTAND seen with vamorolone 6.0 mg/kg/day of 0.05 rises per second is clinically meaningful, at almost twice the published MCID of 0.026 rises per second, and is predictive of a delay of two to three years until loss of ambulation.[69]

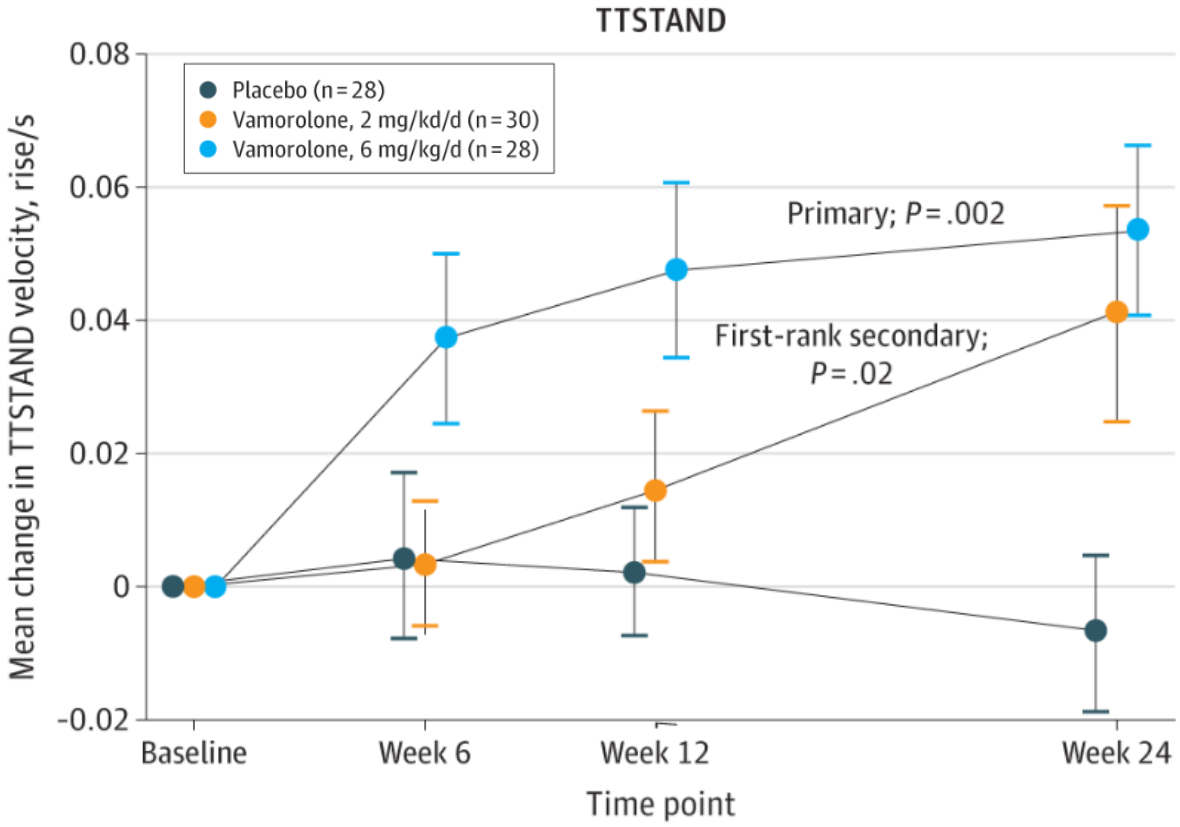
The placebo group showed a stable course with a slight decline relative to baseline, whereas the vamorolone 6.0 mg/kg/day group versus placebo showed improvement by 6 weeks of treatment which was maintained to 24 weeks. Analyses of the mITT population (n=117) versus the per protocol population (n=113) led to similar findings.

Table 17: TTSTAND velocity change from baseline to Week 24: vamorolone 6.0 mg/kg/day versus placebo (mITT-1 population)

TTSTAND Velocity (rises/sec)	**Placebo (n=28)**	**Vamorolone 6.0 mg/kg/day (n=28)**
Baseline, mean (SD)	0.20 (0.06)	0.19 (0.06)
Week 24, mean (SD)	0.19 (0.09)	0.24 (0.08)
Change from baseline at Week 24, mean (SD)	-0.01 (0.06)	0.05 (0.07)
LSM (SE) change from baseline	-0.01 (0.01)	0.04 (0.01)
LSM difference (SE) vs placebo	0.06 (0.02)	
95% CI vs placebo	0.02, 0.10	
p-value vs placebo	0.002	

TTSTAND velocity = 1 / TTSTAND and is expressed as rises/sec. Note that velocity was set to 0 for responses determined to be missing due to disease progression (inability to do the test). Moreover, at the first visit a patient could not perform the test due to disease progression, and at ALL subsequent visits, the raw score was left as missing, and velocity was imputed as 0.
Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; SD – Standard deviation; SE – Standard error; TTSTAND – Time to stand from supine.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

Figure 6: Mean change in TTSTAND velocity at 24 weeks



Abbreviations: Kg – Kilogram; Mg – Milligram; TTSTAND – Time to stand from supine.
Source: Guglieri et al. 2022[4]

The LSM change from baseline in TTSTAND velocity at Week 24 was similar in the vamorolone 6.0 mg/kg/day and prednisone groups with a LSM change from baseline of 0.05 (SE: 0.01) and 0.07 (0.01) rises per second respectively (LSM difference: -0.02 rises per second [95% CI: -0.06-0.02]; *p*=0.2976), as presented in Table 18.[6]

Table 18: TTSTAND velocity change from baseline to Week 24: vamorolone 6.0 mg/kg/day versus prednisone (mITT-1 population)

TTSTAND Velocity (rises/sec)	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	0.22 (0.06)	0.19 (0.06)
Week 24, mean (SD)	0.29 (0.09)	0.24 (0.08)
Change from baseline at Week 24, mean (SD)	0.07 (0.07)	0.05 (0.07)
LSM (SE) change from baseline	0.07 (0.01)	0.05 (0.01)
LSM difference (SE) vs placebo	-0.02 (0.02)	
95% CI vs placebo	-0.06, 0.02	
p-value vs placebo	0.2976	

TTSTAND velocity = 1 / TTSTAND and is expressed as rises/sec. Note that velocity was set to 0 for responses determined to be missing due to disease progression (inability to do the test). Moreover, at the first visit a patient

could not perform the test due to disease progression, and at ALL subsequent visits, the raw score was left as missing and velocity was imputed as 0.
Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; SD – Standard deviation; SE – Standard error; TTSTAND – Time to stand from supine.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

B.2.6.1.2. Secondary efficacy endpoint: TTSTAND velocity with vamorolone 2.0 mg/kg/day

As presented in Table 19, the first secondary efficacy endpoint was met, with TTSTAND velocity being significantly improved with vamorolone 2.0 mg/kg/day compared with placebo at Week 24.[4] The LSM difference for vamorolone 2.0 mg/kg/day from placebo was approximately 0.05 rises per second which was statistically significant (p=0.0171). TTSTAND is seen as a clinically relevant endpoint with good statistical properties for evaluating motor function in clinical studies of patients with early-stage DMD.[79]

Table 19: TTSTAND velocity change from baseline to Week 24: vamorolone 2.0 mg/kg/day versus placebo (mITT-1 population)

TTSTAND Velocity (rises/sec)	Placebo (n=28)	Vamorolone 2.0 mg/kg/day (n=30)
Baseline, mean (SD)	0.20 (0.06)	0.18 (0.05)
Week 24, mean (SD)	0.19 (0.09)	0.23 (0.09)
Change from baseline at Week 24, mean (SD)	-0.01 (0.06)	0.04 (0.07)
LSM (SE) change from baseline	-0.01 (0.01)	0.03 (0.01)
LSM difference (95% CI) vs placebo	0.05 (0.01, 0.08)	
p-value vs placebo	0.0171	

TTSTAND velocity = 1/TTSTAND and is expressed as rises/sec. Note that velocity was set to 0 for responses determined to be missing due to disease progression (inability to do the test). Moreover, at the first visit a patient could not perform the test due to disease progression, and at ALL subsequent visits, the raw score was left as missing, and velocity was imputed as 0.
The LSM estimates are derived from a REML-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: CI – confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg - Milligram; mITT – Modified Intent-to-Treat; SD – Standard deviation; SE – Standard error; TTSTAND – Time to stand from supine.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

B.2.6.1.3. Secondary efficacy endpoint: 6MWT distance

Vamorolone versus prednisone

The mean increase in 6MWT distance for both vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day was seen as clinically meaningful since the mean increase was either approximately 30 metres or >30 metres.[4,84] 6MWT distance was shorter in the

vamorolone 2.0 and 6.0 mg/kg/day group at baseline compared with the prednisone group at baseline. Comparable increases in mean 6MWT distance were seen in the prednisone and vamorolone groups at Week 24; the LSM differences for vamorolone 2.0 mg/kg/day from prednisone and vamorolone 6.0 mg/kg/day from prednisone were not statistically significant (Table 20). Therefore, similar efficacy was seen between vamorolone and prednisone when measured by 6MWT.

Table 20: 6MWT distance change from baseline to Week 24: vamorolone vs prednisone (mITT-1 population)

6MWT distance (metres)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	343.3 (55.84)	316.1 (58.43)	312.5 (56.19)
Week 24, mean (SD)	395.5 (57.32)	349.1 (65.99)	355.9 (50.92)
Change from baseline at Week 24, mean (SD)	39.7 (30.620	31.0 (51.12)	28.8 (49.66)
LSM (SE) change from baseline	48.23 (9.12)	23.88 (9.69)	28.34 (9.56)
LSM difference (SE) vs placebo	NA	-24.35 (13.21)	-19.89 (13.10)
95% CI vs prednisone	NA	-50.61, 1.91	-45.93, 6.15
p-value vs prednisone	NA	0.0687	0.1326

The LSM estimates are derived from a restricted maximum likelihood (REML)-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: 6MWT – 6-minute walk test; CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat;; NA – not applicable; SD - Standard deviation; SE – Standard error.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

Vamorolone versus placebo

There was a statistically significant LSM difference between vamorolone 6.0 mg/kg/day and placebo of approximately 42 metres (p=0.0033; Table 21, Figure 7) and deemed clinically meaningful since it was 40% greater than the minimum longitudinal change in walking ability by 6MWT of 30 metres.[4,84] 6MWT distance was shorter in the vamorolone 6.0 mg/kg/day group compared with the placebo group at baseline but was increased in the vamorolone 6.0 mg/kg/day group and decreased in the placebo group at Week 24 (Table 21). 6MWT distance was also shorter in the vamorolone 2.0 mg/kg/day group compared with the placebo group at baseline but was increased in the vamorolone 2.0 mg/kg/day group and decreased in the placebo group at Week 24 (Table 21). There was a statistically significant LSM difference for vamorolone 2.0 mg/kg/day from placebo of 37 metres (p=0.0089; Table 21) which is also seen as clinically meaningful.[84]

Table 21: 6MWT distance change from baseline to Week 24: vamorolone versus placebo (mITT-1 population)

6MWT distance (metres)	Placebo (n=28)	Vamorolone 6.0 mg/kg/day (n=28)	Vamorolone 2.0 mg/kg/day (n=28)
Baseline, mean (SD)	354.5 (77.59)	312.5 (56.19)	316.1 (58.43)
Week 24, mean (SD)	339.0 (60.90)	355.9 (50.92)	349.1 (65.99)
Change from baseline at Week 24, mean (SD)	-23.9 (59.62)	28.8 (49.66)	31.0 (51.12)
LSM (SE) change from baseline	-13.25 (10.04)	28.34 (9.56)	23.88 (9.69)
LSM difference (SE) vs placebo	NA	41.59 (13.76)	37.12 (13.87)
95% CI vs placebo	NA	14.23, 68.94	9.55, 64.70
p-value vs placebo	NA	0.0033	0.0089

The LSM estimates are derived from a restricted maximum likelihood (REML)-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: 6MWT – 6-minute walk test; CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; NA – Not applicable; SD – Standard deviation; SE –Sstandard error.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

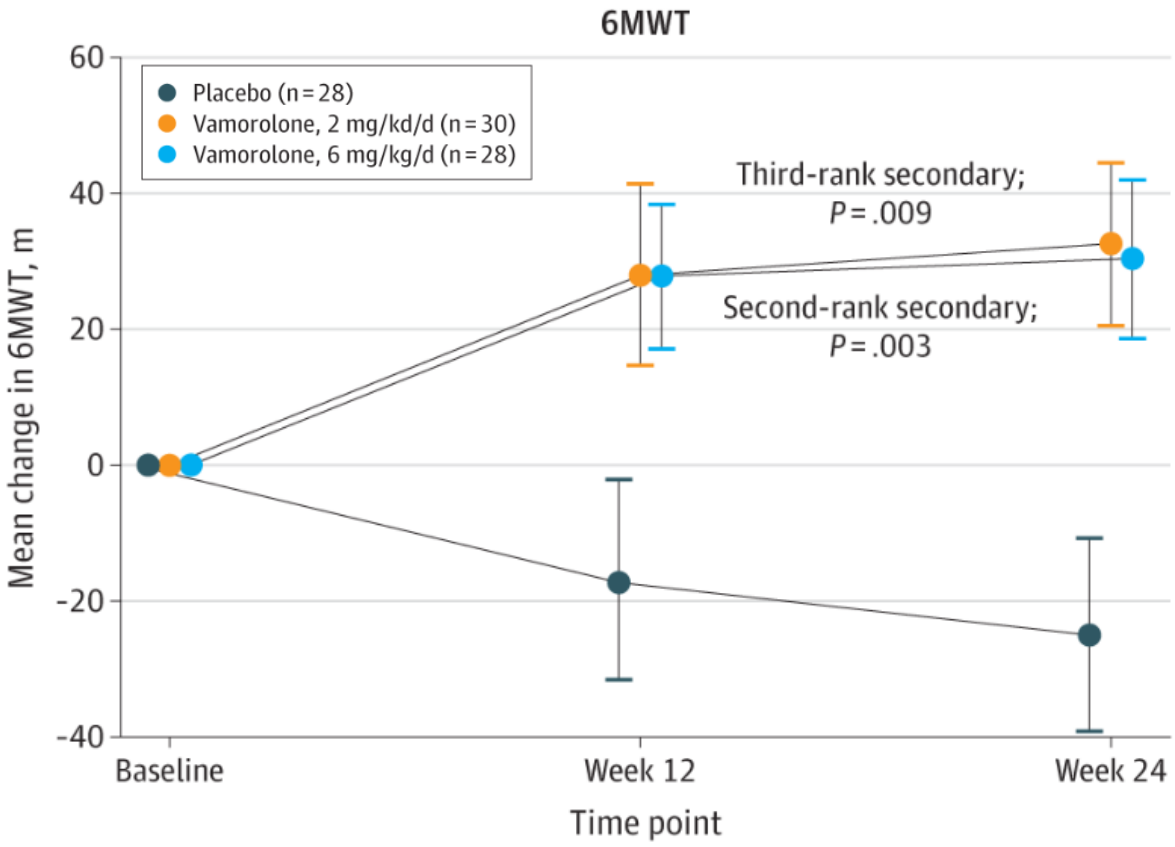


Figure 7: Mean change in 6MWT a0t 24 weeks
Abbreviations: 6MWT – 6-minute walk test; Kg – Kilogram; Mg – Milligram.
Source: Guglieri et al. 2022[4]

B.2.6.1.4. Secondary efficacy endpoint: TTRW velocity

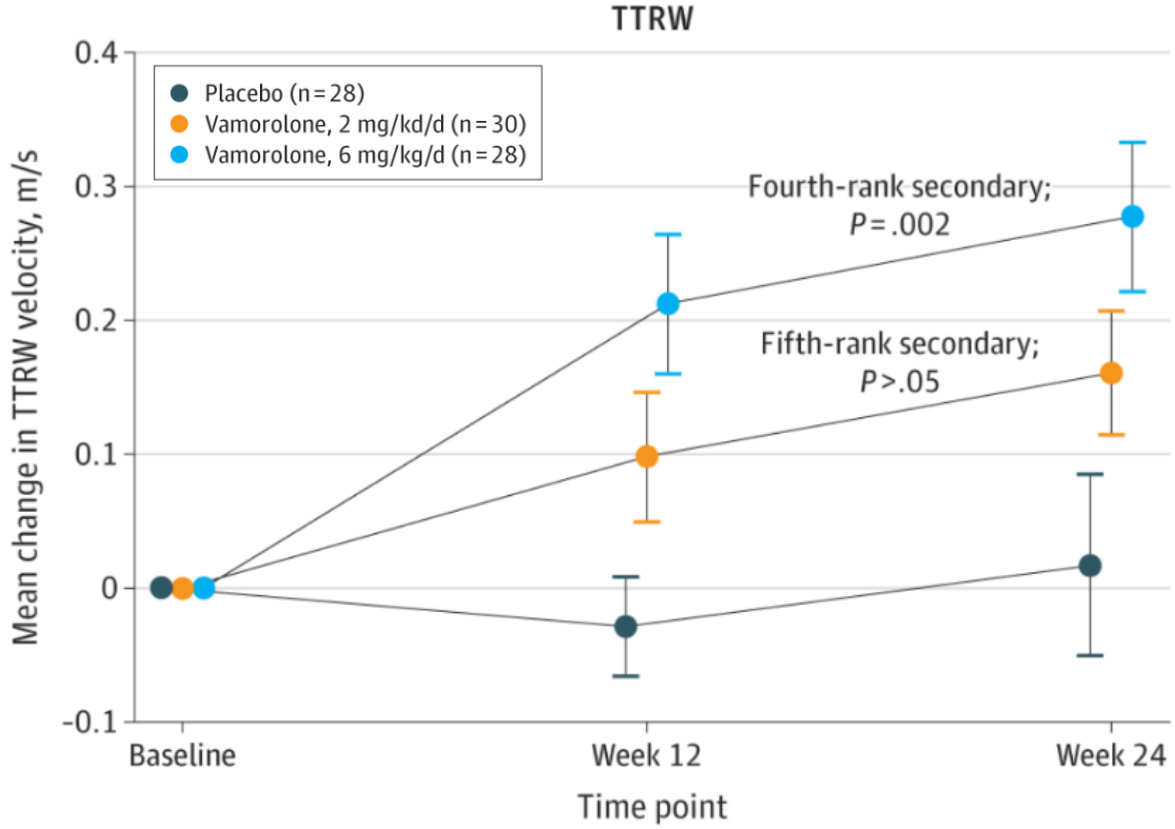
There was a statistically significant difference in TTRW velocity between vamorolone 6.0 mg/kg/day and placebo groups, with an LSM difference of approximately 0.24 metres per second (*p*=0.0018; Table 22, Figure 8).[4,6] The improvement in TTRW velocity with vamorolone 6.0 mg/kg/day is also clinically relevant since it is greater than the MCID for TTSTAND of 0.212 metres per second.[69] TTRW velocity was similar in the vamorolone 2.0 mg/kg/day and placebo groups at baseline and Week 24 (Table 22). There was a numerical improvement, with an LSM difference for vamorolone 2.0 mg/kg/day from placebo of approximately 0.13 metres per second. However, this was not statistically significant (Table 22).

Table 22: TTRW velocity change from baseline to Week 24: vamorolone versus placebo (mITT-1 population)

TTRW Velocity (metres/sec)	Placebo (N=28)	Vamorolone 6.0 mg/kg/day (n=30)	Vamorolone 2.0 mg/kg/day (n=30)
Baseline, mean (SD)	1.74 (0.35)	1.60 (0.36)	1.56 (0.29)
Week 24, mean (SD)	1.77 (0.44)	1.89 (0.41)	1.72 (0.37)
Change from baseline at Week 24, mean (SD)	0.02 (0.33)	0.28 (0.28)	0.16 (0.23)
LSM (SE) change from baseline	0.01 (0.06)	0.26 (0.05)	0.14 (0.06)
LSM difference (SE) vs placebo	NA	0.24 (0.08)	0.13 (0.08)
95% CI vs placebo	NA	0.09, 0.39	-0.03, 0.28
p-value vs placebo	NA	0.00	0.10

The LSM estimates are derived from a REML-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; MMRM – mixed model repeated measures; NA – not applicable; REML – restricted maximum likelihood; SD - Standard deviation; SE – Standard error; TTRW – Time to run/walk 10m.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

Figure 8: Mean change in TTRW velocity at 24 weeks



Abbreviations: TTRW – Time to run/walk 10 metres; Kg – Kilogram; Mg – Milligram.
Source: Guglieri et al. 2022[4]

B.2.6.1.5. Exploratory endpoint: TTCLIMB velocity

TTCLIMB velocity was similar in the vamorolone 6.0 mg/kg/day, 2.0 mg/kg/day, and placebo groups at baseline and was increased in each of the vamorolone groups and slightly decreased in the placebo group at Week 24 (Table 23, Figure 9).[4,6] The LSM difference was statistically significant at 0.07 tasks per second for vamorolone 6.0 mg/kg/day from placebo (p=0.0008, Table 23). This was almost double the MCID of 0.035 tasks per second, and 0.06 tasks per second for vamorolone 2.0 mg/kg/day from placebo (Table 23).[69]

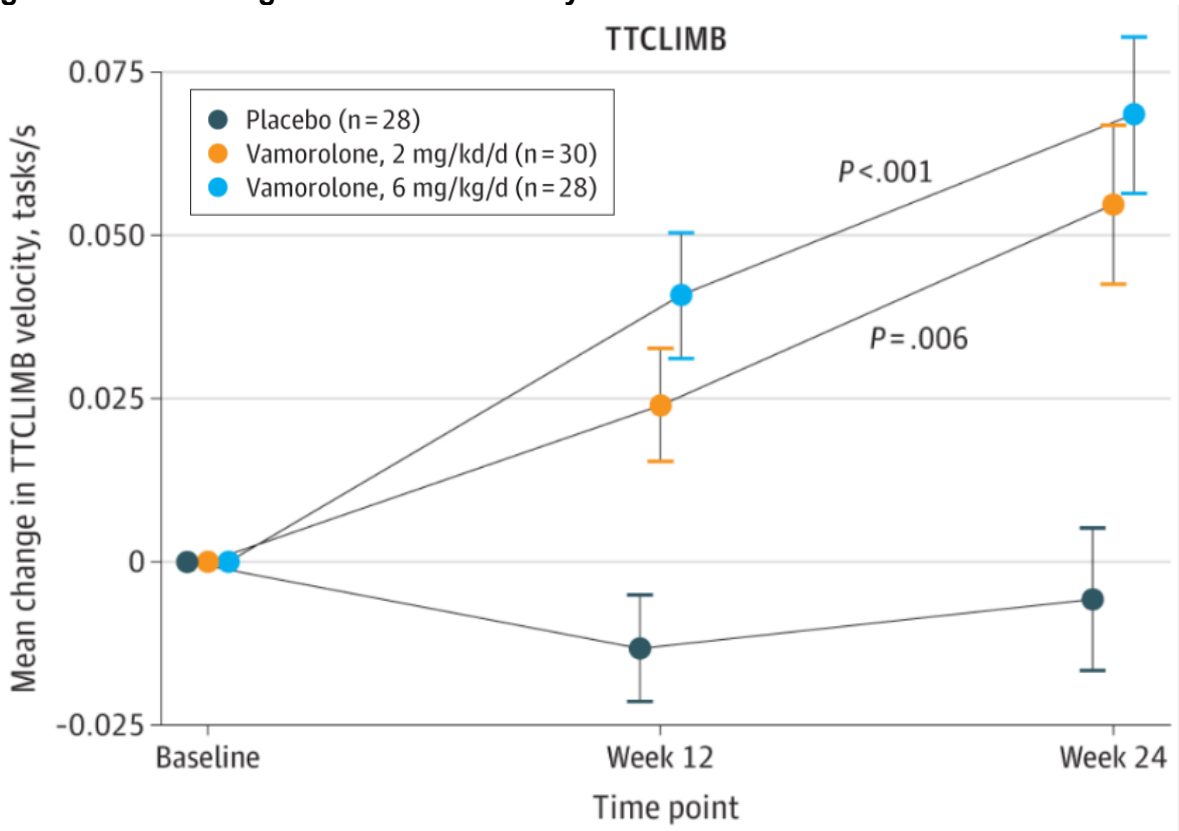
Table 23: Change from baseline to Week 24 in TTCLIMB velocity: vamorolone vs placebo (mITT-1 population)

TTCLIMB velocity (tasks/sec)	Placebo (n=28)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	0.25 (0.09)	0.20 (0.05)	0.21 (0.09)
Week 24, mean (SD)	0.25 (0.12)	0.26 (0.08)	0.27 (0.10)
Change from baseline at Week 24, mean (SD)	-0.01 (0.05)	0.06 (0.06)	0.07 (0.06)
LSM (SE) change from baseline	-0.01 (0.02)	0.05 (0.02)	0.06 (0.01)

TTCLIMB velocity (tasks/sec)	Placebo (n=28)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
LSM difference (SE) vs placebo	NA	0.06 (0.02)	0.07 (0.02)
95% CI vs placebo	NA	0.02, 0.1	0.03, 0.11
p-value vs placebo	NA	0.0056	0.0008

TTCLIMB velocity = 1 / TTCLIMB and is expressed as tasks/sec. Note that velocity is set to 0 for responses determined to be missing due to disease progression (inability to do the test). Moreover, at the first visit a patient could not perform the test due to disease progression, and at ALL subsequent visits, the raw score was left as missing, and velocity was imputed as 0.
Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; NA – Not applicable; SD - Standard deviation; SE – Standard error; TTCLIMB – Time to climb 4 stairs.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

Figure 9: Mean change in TTCLIMB velocity at 24 weeks



Abbreviations: Kg – Kilogram; Mg – Milligram; TTCLIMB – time to climb 4 stairs.
Source: Guglieri et al. 2022[4]

B.2.6.1.6. Exploratory endpoint: NSAA score

There were statistically significant and clinically meaningful increases in NSAA score with vamorolone at Week 24. NSAA score was similar in the vamorolone and placebo groups at baseline and was increased in the vamorolone groups and slightly decreased in the placebo group at Week 24 (Table 24, Figure 10).[4,6] The LSM difference was 3.6 points for vamorolone 6.0 mg/kg/day from placebo (p<0.0001) and 3.2 points for vamorolone 2.0 mg/kg/day from placebo (p=0.0003; Table 24). The

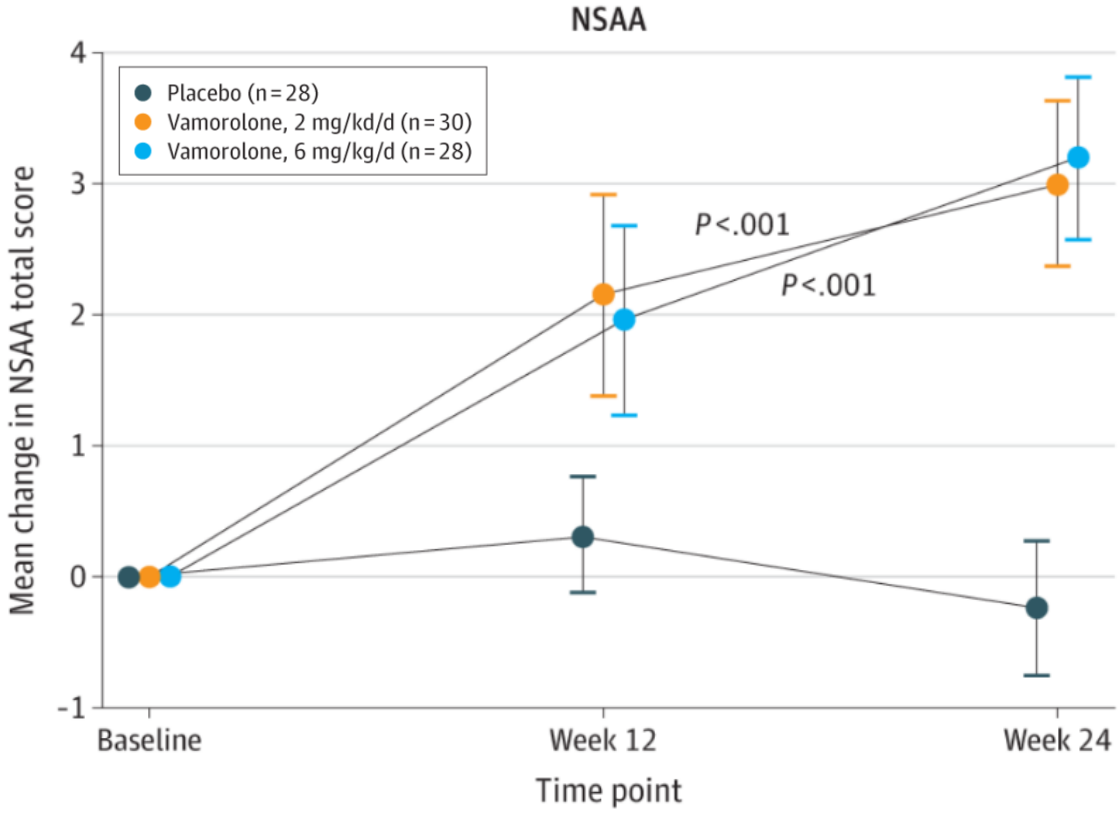
increases in each of the vamorolone groups at Week 24 (approximately three points) were also clinically meaningful since it is greater than the MCID for NSAA total score of 2.32 points.[85]

Table 24: Change from baseline to Week 24 in NSAA score: vamorolone vs placebo (mITT-1 population)

NSAA score	Placebo (n=28)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	18.9 (5.30)	17.2 (4.66)	18.9 (4.07)
Week 24, mean (SD)	18.9 (5.60)	20.4 (5.62)	22.0 (5.17)
Change from baseline at Week 24, mean (SD)	-0.2 (2.57)	3.0 (3.11)	3.2 (3.18)
LSM (SE) change from baseline	-0.73 (0.62)	2.52 (0.63)	2.85 (0.61)
LSM difference (SE) vs placebo	NA	3.25 (0.87)	3.57 (0.84)
95% CI vs placebo	NA	1.53, 4.97	1.90, 5.25
p-value vs placebo	NA	0.0003	<0.0001

Note: NSAA total score was only calculated for a patient if all sub-scores were non-missing at visit.
Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; NA – Not applicable; NSAA – North Star Ambulatory Assessment; SD -Standard deviation; SE – Standard error.
Source: Guglieri et al. 2022[4]; VISION-DMD CSR[6]

Figure 10: Mean change in NSAA total score at 24 weeks



Abbreviations: Kg – Kilogram; Mg – Milligram; NSAA - North Star Ambulatory Assessment.
Source: Guglieri et al. 2022[4]

B.2.6.1.7. Exploratory endpoint: Knee extension and elbow flexor muscle strength

Knee extension muscle strength was lower at baseline in the vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day groups compared with the placebo group and improved in each of these groups at Week 24 (Table 25).[6] However, neither of the LSM differences for vamorolone from placebo were statistically significant at Week 24.

Table 25: Knee extension muscle strength (mITT-1 population)

	Placebo (n=28)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline (kg), mean (SD)	5.57 (2.04)	5.30 (1.81)	5.47 (1.74)
Week 24, mean (SD)	5.64 (2.37)	5.37 (2.15)	5.52 (2.22)
Change from baseline at Week 24, mean (SD)	0.15 (2.10)	0.12 (1.32)	0.28 (1.93)
LSM (SE) change from baseline	-0.06 (0.36)	0.00 (0.3758)	0.01 (0.36)
LSM difference (SE) vs placebo	NA	0.07 (0.51)	0.16 (0.49)
95% CI vs placebo	NA	-0.95, 1.08	-0.82, 1.14
p-value vs placebo	NA	0.8987	0.7411

Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; NA - Not applicable; SD - Standard deviation; SE – Standard error.
Source: VISION-DMD CSR[6]

Similarly, elbow flexor muscle strength was lower at baseline in the vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day groups compared with the placebo group (Table 26), and increased in the vamorolone groups and decreased in the placebo group at Week 24 (Table 26).[6] However, neither of the LSM differences for vamorolone from placebo were statistically significant at Week 24.

Table 26: Elbow flexor muscle strength (mITT-1 population)

	Placebo (n=28)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline (kg), mean (SD)	3.38 (1.49)	2.68 (0.81)	2.86 (0.78)
Week 24, mean (SD)	3.26 (1.33)	3.48 (0.94)	3.34 (1.13)
Change from baseline at Week 24, mean (SD)	-0.15 (1.41)	0.74 (1.23)	0.50 (1.16)
LSM (SE) change from baseline	0.02 (0.21)	0.61 (0.22)	0.43 (0.20)
LSM difference (SE) vs placebo	NA	0.59 (0.30)	0.41 (0.28)
95% CI vs placebo	NA	-0.01, 1.19	-0.15, 0.98
p-value vs placebo	NA	0.0546	0.1485

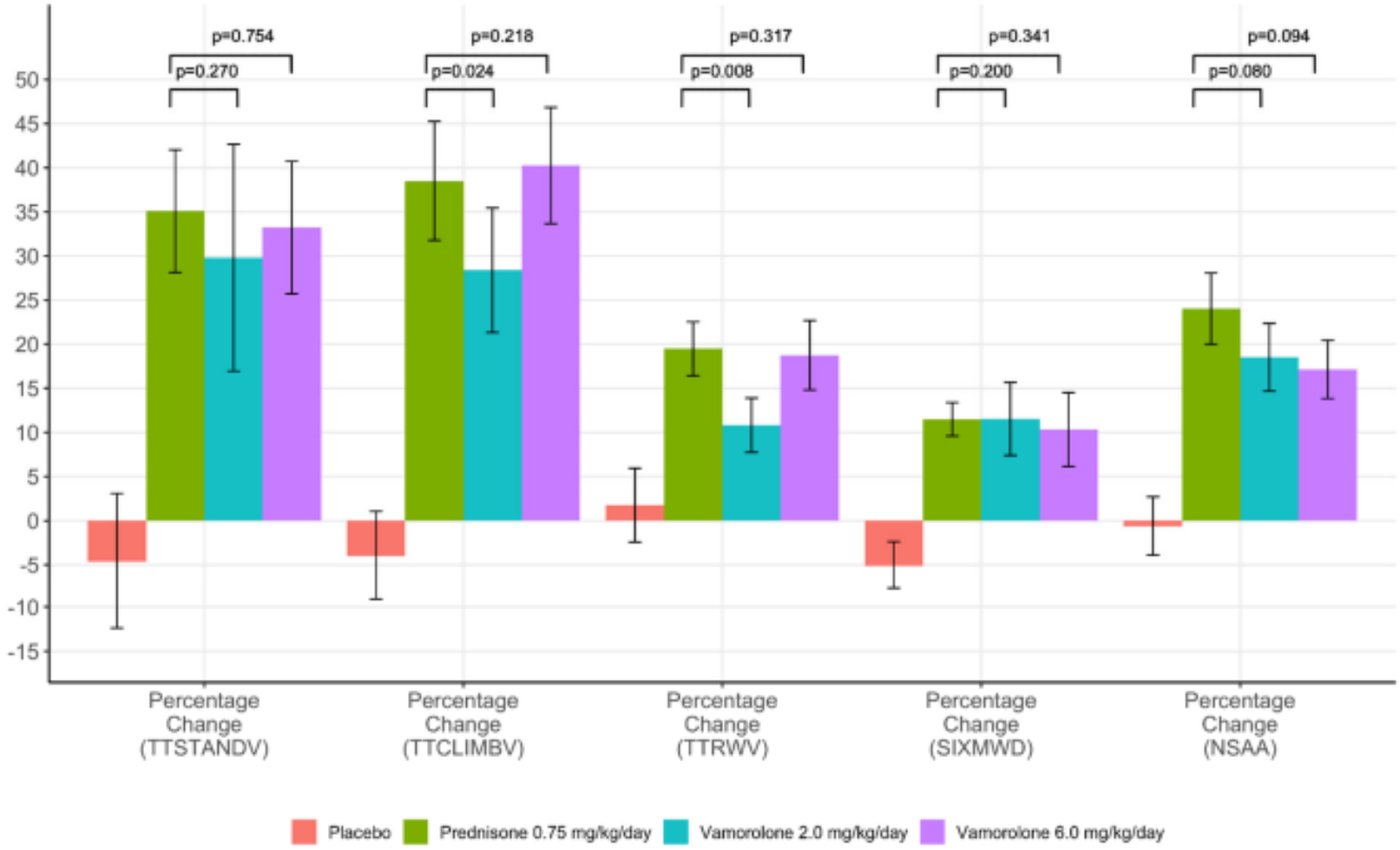
Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; NA – Not applicable; SD - Standard deviation; SE – Standard error.
Source: VISION-DMD CSR[6]

B.2.6.1.8. Exploratory endpoint: Percentage change from baseline at Week 24 for all efficacy endpoints

To compare the efficacy of vamorolone 2.0 mg/kg/day with 6.0 mg/kg/day, the mean percentage change from baseline for all efficacy endpoints was compared, as presented in Figure 11. This was numerically greater with vamorolone 6.0 mg/kg/day compared with 2.0 mg/kg/day for all endpoints except 6MWT distance and NSAA, indicating that the higher-dose may be more effective.[4] However, these differences did not appear to be clinically meaningful.

A similar comparison was made between vamorolone and prednisone. Percent changes from baseline at Week 24 in TTSTAND, TTSTAND velocity, 6MWT distance, TTRW velocity, and TTCLIMB velocity were similar for vamorolone 6.0 mg/kg/day compared with prednisone (Figure 11).[4] Mean change from baseline at Week 24 in TTSTAND velocity, TTCLIMB velocity, NSAA and 6MWT distance was also similar for vamorolone 2.0 mg/kg/day compared with prednisone. This indicates that vamorolone has a similar efficacy to prednisone. TTRW velocity was greater in the prednisone group compared to the vamorolone 2.0 mg/kg/day group.

Figure 11: Comparisons between vamorolone, placebo and prednisone in time tests, analysed as percentage changes from baseline



Abbreviations :Kg – Kilogram; Mg – Milligram; NSAA – North Star Ambulatory Assessment SIXMWD – 6-minute walk test; TTCLIMBV – Time to climb 4 stairs velocity; TTRWV – Time to run/walk 10m velocity; TTSTANDV – Time to stand from supine velocity.
Source: Guglieri et al. 2022[4]

B.2.6.1.9. Patient-reported outcomes

Results for both the PODCI and the TSQM showed no significant differences between vamorolone and the placebo groups.[4] The PARS III questionnaire suggested that vamorolone 2.0 mg/kg/day showed better adjustment for anxiety and depression compared with prednisone, however this was not adjusted for multiple testing.

B.2.6.2. Week 48 results, VISION-DMD

The objectives of period 2 were to evaluate the efficacy and safety of continuous 48-weektreatment with vamorolone, and to assess vamorolone efficacy and safety in crossover patients. The treatment benefits established with vamorolone 6.0 mg/kg/day at Week 24 were maintained at Week 48.[5]

B.2.6.2.1. Secondary efficacy endpoint: TTSTAND velocity with vamorolone 6.0 mg/kg/day and 2.0 mg/kg/day

The clinically meaningful improvement seen with vamorolone 6.0 mg/kg/day at Week 24 in TTSTAND velocity was maintained at Week 48 as shown by the similar LSM changes from baseline at Week 24 and Week 48; a slight decrease was seen at Week 48 for vamorolone 2.0 mg/kg/day (Table 27).[5] At Week 48, TTSTAND velocity was significantly faster with vamorolone 6.0 mg/kg/day compared with 2.0 mg/kg/day.

Table 27: Change from baseline at Week 24 and Week 48 in TTSTAND velocity with vamorolone (mITT-2 population)

TTSTAND velocity (rises/sec)	LSM (SE)	LSM Difference (SE) [95% CI]	p-value
Week 24 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	0.05 (0.01) vs. 0.03 (0.01)	0.03 (0.02) [-0.01, 0.06]	0.1478
Week 48 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	0.04 (0.01) vs. -0.01 (0.01)	0.05 (0.02) [0.01, 0.09]	0.0099

The LSM estimates are derived from a REML-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day and vamorolone 6.0 mg/kg/day), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, 24, 34, 40 and 48) along with the treatment-by-week interaction. An unstructured covariance structure is used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; MMRM – mixed model repeated measures; REML – restricted maximum likelihood; SE – Standard error; TTSTAND – Time to stand from supine; vs – Versus.

Source: Hoffman et al. 2023[5]; VISION-DMD CSR[6]

B.2.6.2.2. Secondary efficacy endpoint: 6MWT distance

An additional improvement in 6MWT distance was seen from Week 24 to Week 48 with vamorolone 6.0 mg/kg/day (38.6 metres to 49.7 metres) whereas a decrease was seen with vamorolone 2.0 mg/kg/day (29.3 metres to 14.9 metres) (Table 28).[5,6] At Week 48, 6MWT distance was significantly longer with vamorolone 6.0 mg/kg/day compared with 2.0 mg/kg/day.

Table 28: Change from baseline at Week 24 and Week 48 in 6MWT distance with vamorolone (mITT-2 population)

6MWT distance (metres)	LSM (SE)	LSM Difference (SE) [95% CI]	*p*-value
Week 24 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	38.57 (10.30) vs. 29.30 (10.50)	9.27 (14.08) [-19.10, 37.65]	0.5137
Week 48 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	49.68 (12.54) vs. 14.92 (12.34)	34.76 (17.02) [0.45, 69.08]	0.0472

The LSM estimates are derived from a REML-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day and vamorolone 6.0 mg/kg/day), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, 24, 34, 40 and 48) along with the treatment-by-week interaction. An unstructured covariance structure is used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: 6MWT – 6-minute walk test; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; MMRM – Mixed model repeated measures; REML – Restricted maximum likelihood; SE – Standard error; vs – Versus.
Source: Hoffman et al. 2023[5]; VISION-DMD CSR[6]

B.2.6.2.3. Secondary efficacy endpoint: TTRW velocity

The clinically meaningful improvement seen with vamorolone 6.0 mg/kg/day at Week 24 in TTRW velocity was maintained at Week 48 (0.31 metres per second to 0.25 metres per second) as shown by the similar LSM changes from baseline at Week 24 and Week 48 (Table 29).[5,6] No significant difference in TTRW velocity was seen between the vamorolone groups.

Table 29: Change from baseline at Week 24 and Week 48 in TTRW velocity with vamorolone (mITT-2 population)

TTRW velocity (metres/sec)	LSM (SE)	LSM Difference (SE) [95% CI]	p-value
Week 24 Change from Baseline			

Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	0.31 (0.05) vs. 0.17 (0.05)	0.13(0.070) [-0.01, 0.28]	0.0631
Week 48 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	0.25 (0.07) vs. 0.15 (0.07)	0.10 (0.10) [-0.13, 0.30]	0.3492

The LSM estimates are derived from a REML-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day and vamorolone 6.0 mg/kg/day), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, 24, 34, 40 and 48) along with the treatment-by-week interaction. An unstructured covariance structure is used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; MMRM – Mixed model repeated measures; REML – Restricted maximum likelihood; SE – Standard error; TTRW – Time to run/walk 10m; vs – Versus.
Source: Hoffman et al. 2023[5]; VISION-DMD CSR[6]

B.2.6.2.4. Exploratory endpoint: NSAA score

The clinically meaningful improvements seen with vamorolone 2.0 and 6.0 mg/kg/day in NSAA score at Week 24 were maintained at Week 48 as shown by the similar LSM changes from baseline in each of these groups at Week 24 and Week 48 (Table 30).[5,6] No significant difference in NSAA score was seen between the vamorolone groups for NSAA score.

Table 30: Change from baseline at Week 24 and Week 48 in NSAA score with vamorolone (mITT-2 population)

NSAA Score	LSM (SE)	LSM Difference (SE) [95% CI]	*p*-value
Week 24 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	3.09 (0.66) vs. 2.71 (0.67)	0.39 (0.90) [-1.43, 2.21]	0.6684
Week 48 Change from Baseline			
Vamorolone 6.0 mg/kg/day vs. Vamorolone 2.0 mg/kg/day	3.08 (0.83) vs. 2.59 (0.83)	0.49 (1.14) [-1.80, 2.78]	0.6694

The LSM estimates are derived from a REML-based MMRM model with enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day and vamorolone 6.0 mg/k), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, 24, 34, 40 and 48) along with the treatment-by-week interaction. An unstructured covariance structure is used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT – Modified Intent-to-Treat; MMRM – Mixed model for repeated measures; NSAA – North Star Ambulatory Assessment; REML – Restricted maximum likelihood; SE – Standard error; vs – Versus.
Source: Hoffman et al. 2023[5]; VISION-DMD CSR[6]

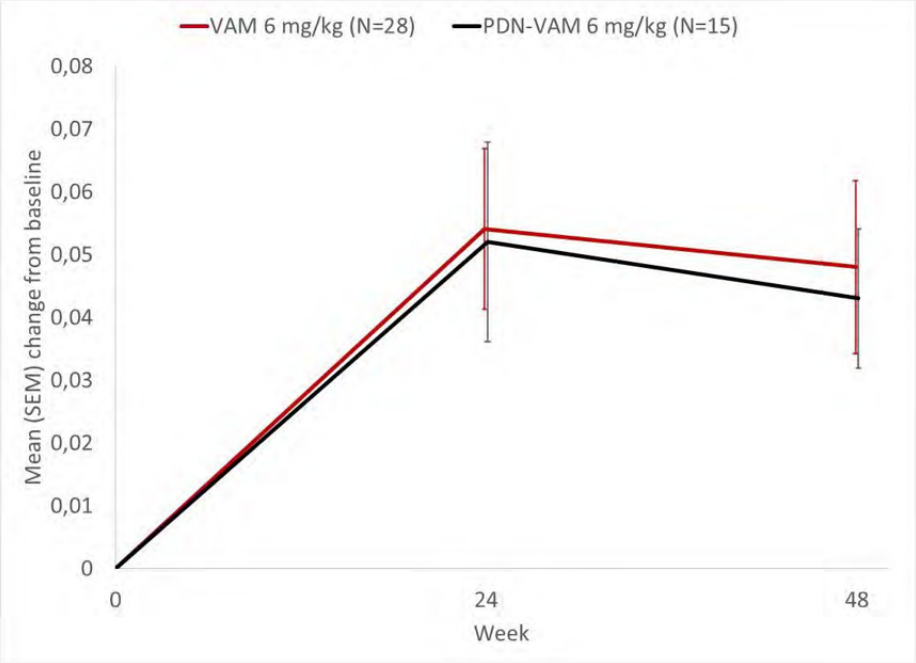
B.2.6.2.5. Switch from prednisone to vamorolone

The treatment benefits seen with prednisone at Week 24 were maintained to Week 48 when patients were switched to vamorolone 6.0 mg/kg/day. No

decrease in mean TTSTAND velocity (Figure 12), TTRW (Figure 14) and TTCLIMB velocity or NSAA score (

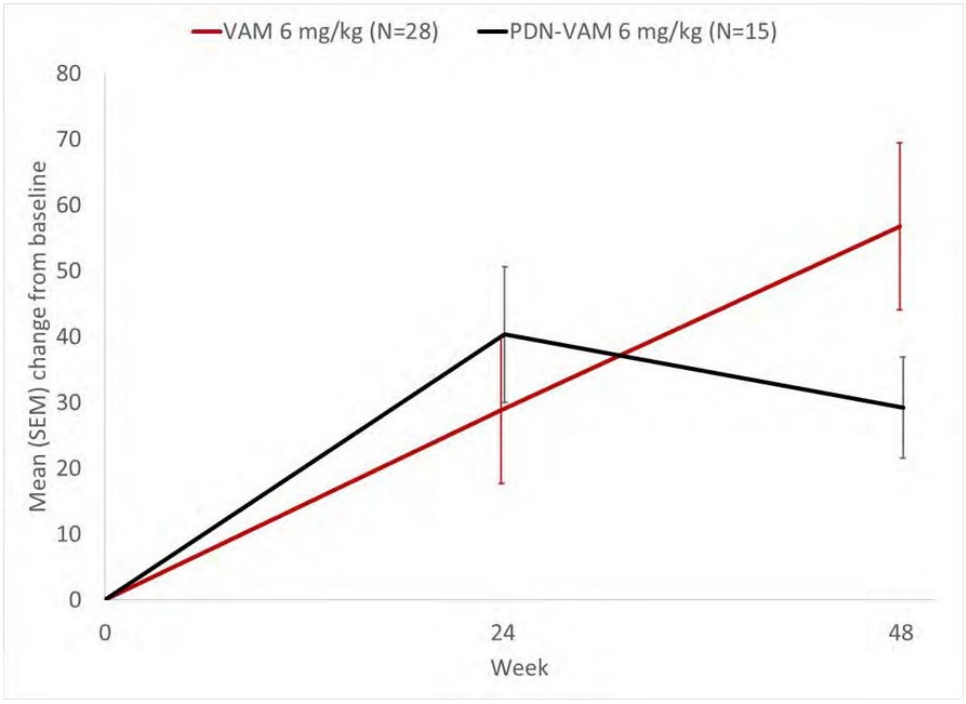
Figure 15) was seen following the switch from prednisone to vamorolone 6.0 mg/kg/day, and 6MWT distance increased following the switch from prednisone to vamorolone 6.0 mg/kg/day (Figure 13).[6]

Figure 12: TTSTAND velocity (rises/sec) following the switch from prednisone to vamorolone (descriptive statistics, mITT-2 population)



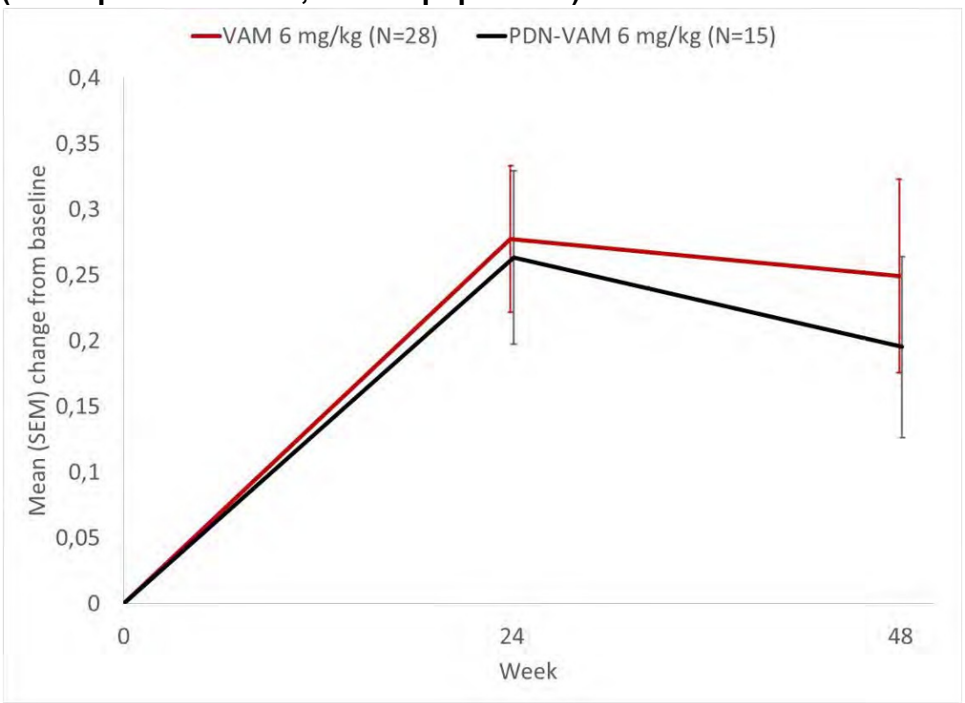
Abbreviations: Kg – Kilogram; Mg – Milligram; mITT – Modified Intent-to-Treat; PDN – Prednisone; SEM – Standard error of the mean; TTSTAND – Time to stand from supine; VAM – Vamorolone.
Source: VISION-DMD CSR[6]

Figure 13: 6MWT distance following the switch from prednisone to vamorolone (descriptive statistics, mITT-2 Population)



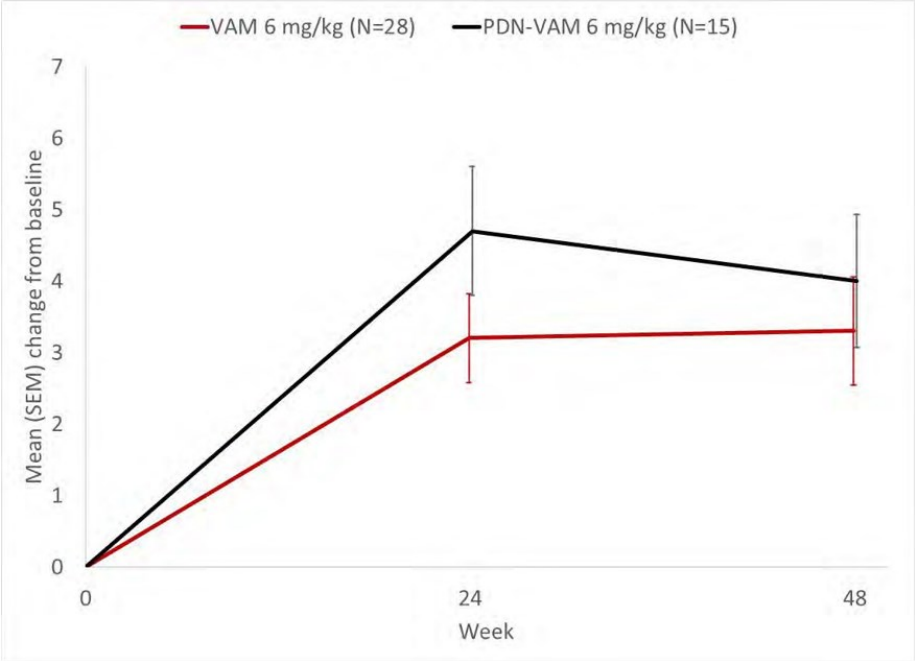
Abbreviations: 6MWT – 6-minute walk test; Kg – Kilogram; Mg – Milligram; mITT – Modified Intent-to-Treat; PDN – Prednisone; SEM – Standard error of the mean; VAM – Vamorolone.
Source: VISION-DMD CSR[6]

Figure 14: TTRW velocity following the switch from prednisone to vamorolone (descriptive statistics, mITT-2 population)



Abbreviations: Kg – Kilogram; Mg – Milligram; mITT – Modified Intent-to-Treat; PDN – Prednisone; SEM – Standard error of the mean; TTRW – Time to run/walk 10m; VAM – Vamorolone.
Source: VISION-DMD CSR[6]

Figure 15: NSAA total score following the switch from prednisone to vamorolone (descriptive statistics, mITT-2 population)



Abbreviations: Kg – Kilogram; Mg – Milligram; mITT – Modified Intent-to-Treat; NSAA – North Star Ambulatory Assessment; PDN – Prednisone; SEM – Standard error of the mean; VAM – Vamorolone.
Source: VISION-DMD CSR[6]

B.2.6.2.6. Simulation modelling of dosing

As noted in the SmPC, patients treated with vamorolone 6 mg/kg/day may be down-titrated to 4 mg/kg/day.[11] A modelling and simulation-based analysis predicted similar efficacy for vamorolone 6 mg/kg/day and 4 mg/kg/day. Partial efficacy was predicted for vamorolone 2 mg/kg/day after 48 weeks, as presented in Figure 17. As shown, the efficacy of vamorolone across different doses is expected to be similar.

Figure 16: Predicted placebo-corrected efficacy for different treatments

Source: Vamorolone SmPC[11]

B.2.6.3. VBP15-LTE

Following completion of VBP15-003, (Figure 4), 46 patients continued in the extension study VBP15-LTE and 41 patients (89.1%) completed the 2-year LTE treatment period; five patients withdrew for reasons unrelated to the study drug.[68] Analysis of treatment efficacy focused on 23 patients receiving higher-dose vamorolone who were initially assigned and maintained on 2.0 mg/kg/day or more for up to 30 months during the dose-finding study (6 months) and LTE study (24 months). A summary of efficacy outcomes is presented in Table 31.

Table 31: Summary of efficacy outcomes from VBP15-LTE

Parameter	Results from baseline to 30 months
TTSTAND velocity (n=23)	0.21 (0.07) rises/s versus 0.19 (0.12) rises/s.
TTCLIMB velocity (n=18)	0.04 tasks/s; 95% CI: -0.05 to 0.12 tasks/s.
TTRW velocity (n=18)	0.06 m/s; 95% CI: −0.27 to 0.39 m/s.
6MWT (n=15)	32.0 m; 95% CI: -18.95 to 82.95 m.
NSAA (n=18)	1.6; 95% CI: -2.92 to 6.14.
PODCI upper extremity and physical function (n=18)	No statistically significant change.
PODCI transfer and basic mobility (n=19)	No statistically significant change.
Dose-related efficacy	Participants initiated on higher-dose vamorolone (i.e., those with early starts) had better clinical outcomes at 6 months compared with those initially treated with low doses (i.e., those with delayed starts). At 6, 18, and 30 months, the means of all five motor outcome measures were increased for participants with early starts compared with those with delayed starts, although not all these differences were statistically significant.

Abbreviations: 6MWT – 6-metre walk test; CI – Confidence interval; LTE – Long-term extension; NSAA – North Star Ambulatory Assessment; PODCI - Paediatric Outcomes Data Collection Instrument; TTCLIMB – Time to climb 4 steps; TTRW – Time to run/walk 10 metres; TTSTAND – Time to standing from supine.
Source: Mah et al., 2022[68]

In longitudinal comparisons of mean TTSTAND, TTRW, TTCLIMB velocity and TTSTAND velocity from baseline to end of follow-up, the LTE group and DNHS group were not significantly different.[68] The non-parametric maximum likelihood estimator (NPMLE) estimate of time to reach a TTSTAND milestone of 10 seconds or more for 108 participants in NSUK who had not experienced this event by baseline was similar to that for participants in DNHS and participants in the LTE study receiving higher doses. BMI Z-score change (0.002 SD/mo (95% CI: -0.006 to 0.010); p=0.58) was not significantly different between the higher-dose vamorolone group versus the DNHS group. The comparison of the NSAA scores between the study group and the NSUK group who received glucocorticoids at 2-years follow-up were not statistically significantly different.

B.2.7. Subgroup analysis; pivotal study (VISION-DMD)

In the VISION-DMD study, pre-planned analyses of TTSTAND velocity for vamorolone 6.0 mg/kg/day versus placebo were conducted for the following subgroups:

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Due to baseline imbalance, an additional post-hoc subgroup analysis was conducted in patients who had a baseline [redacted]

Statistical analysis was as per the primary efficacy endpoint, using the same MMRM without imputed data. See Section evidence more information.

[redacted][6][redacted](Figure 17).

Figure 17: Forest plot TTSTAND velocity in subgroups (mITT-1 population)

Abbreviations: 6MWT – 6-minute walk test; Mg – Milligram; mITT – Modified Intent-to-Treat; TTSTAND – Time to stand from supine.
Source: VISION-DMD CSR[6]

B.2.8. Meta-analysis

A meta-analysis was not conducted as the VISION-DMD study captures clinical evidence for the key comparator of interest.

B.2.9. Indirect and mixed treatment comparisons

A formal indirect treatment comparison was not conducted as the VISION-DMD study captures all clinical evidence of interest.

A post-hoc, cross-study, indirect comparison, was conducted to compare vamorolone with prednisone and deflazacort.[70] Data from two double-blind studies VISION-DMD[4] and FOR-DMD[76], and one open-label study VBP15-LTE[68] were analysed. The data from the double-blind studies were compared during the 1-year treatment period (VISION-DMD versus FOR-DMD). The long-term data were then compared during the subsequent 1.5-year treatment period

(FOR-DMD versus VBP15-LTE). These external comparators were used to assess the safety and efficacy of vamorolone compared with corticosteroid regimens that were administered for a longer duration (48 weeks) than the internal prednisone control in VISION-DMD (24 weeks). The FOR-DMD Co-Study Chair, Dr Michela Guglieri, was also Study Chair for VISION-DMD and outcome measures and assessment protocols were harmonised in the design of VISION-DMD to enable comparisons between the two studies.

FOR-DMD was a randomised, prospective, multicentre, double-blind study of corticosteroid regimens in boys with DMD. This indirect comparison compared patients treated with prednisone 0.75 mg/kg/day (n=55) or deflazacort 0.9 mg/kg/day (n=49) in FOR-DMD to those treated with vamorolone 2.0 mg/kg/day (n=28) or vamorolone 6.0 mg/kg/day (n=28) in the VISION-DMD study (up to 48 weeks) or treated with 2.0–6.0 mg/kg/day flexible dosing in the VBP15-LTE study (n=46; up to 2.5 years).[70] The patients meeting the common inclusion criteria of all studies (patients with confirmed DMD aged 4 to <7 years at baseline, able to walk independently and complete the time to stand test without assistance) were extracted for the analysis. The FOR-DMD study was selected as the external comparator for this study because the studies were similar with respect to the following: harmonisation of motor outcome measures and assessment protocols; overlapping recruitment sites and study management; harmonised treatment regimen (same prednisone and placebo tablets used for both studies; same treatment bands for prednisone dose); overlap of treatment duration (48-week assessment); and similar inclusive/exclusion criteria and subject population.

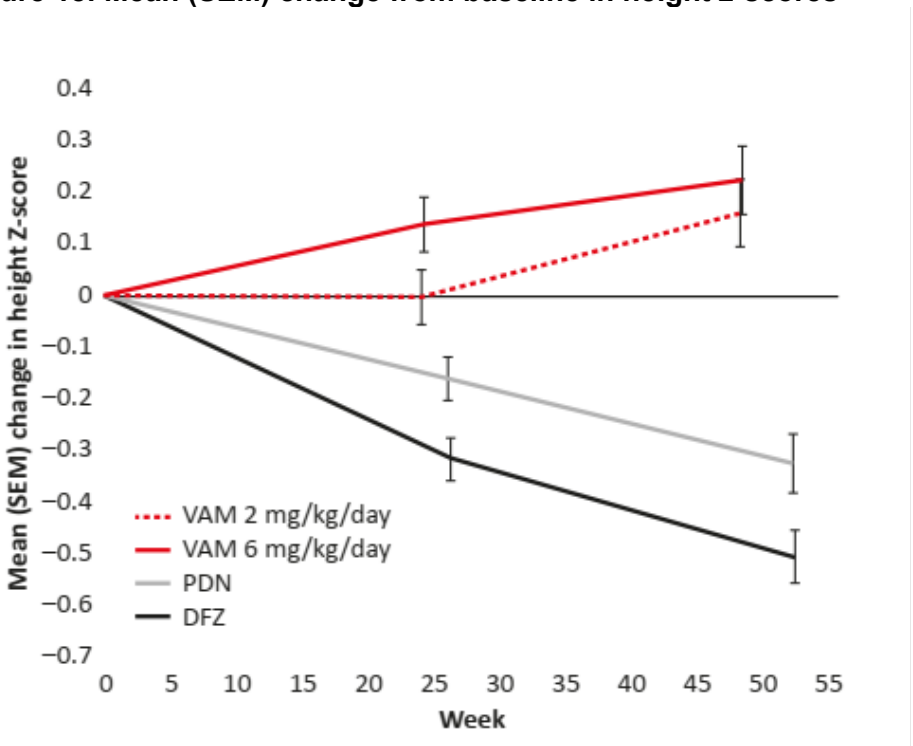
Height and BMI Z-scores were calculated using the Centre for Disease Control and Prevention (CDC) growth data.[70] Changes from baseline and annualised slopes of changes were analysed with mixed model for repeated measures or as cumulative response plots.

The BMI Z-scores were analysed both as actual changes from baseline and as conditional changes from baseline by calculating baseline-adjusted changes in

BMI Z-scores.[86] An annual change >1 standard deviation score (SDS) in the conditional BMI was defined as a clinically significant change.

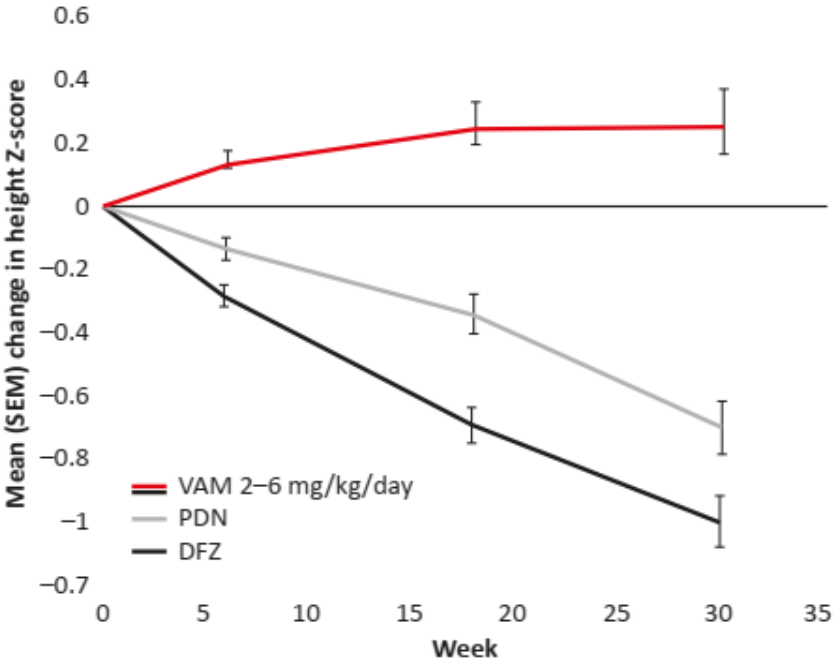
The results of this indirect comparison demonstrate that over 1 to 2.5 years of treatment with deflazacort or prednisone, height z-scores decreased with deflazacort and prednisone, but increased with vamorolone in patients with DMD as shown in Figure 18.[70] BMI numerically increased less with vamorolone than deflazacort and prednisone during the same period.

Figure 18: Mean (SEM) change from baseline in height z-scores



Abbreviations: DFZ – deflazacort; kg – kilogram; mg – milligram; PDN – prednisone; SEM – standard error of the mean; VAM – vamorolone.
Source: Ward et al. 2022[70]

Figure 19: Mean (SEM) change from baseline in height Z-scores



Abbreviations: DFZ – Deflazacort; Kg – Kilogram; Mg – Milligram; PDN – Prednisone; SEM –Standard error of the mean; VAM – Vamorolone.
Source: Ward et al. 2022[70]

B.2.10. Adverse reactions

B.2.10.1. Week 24 results, VISION-DMD

B.2.10.1.1. Exposure to vamorolone

Duration of exposure during period 1 of the VISION-DMD study (24-weeks) was similar for both vamorolone arms (2.0 mg/kg/day and 6.0 mg/kg/day) when compared with the placebo and prednisone groups, with all four groups having a median treatment duration of 168 days, as presented in Table 32.[6] Approximately 93% of patients in the vamorolone 2.0 mg/kg/day group and 96% in the vamorolone 6.0 mg/kg/day group, placebo and prednisone groups were exposed to the drug for 20 to 24 weeks. Minimum exposure time in the vamorolone 6.0 mg/kg/day group was over double the minimum exposure time of prednisone (122 days to 50 days respectively), suggesting greater treatment compliance.

Table 32: 24-week exposure

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Median duration of exposure, days (range)*	168 (51 – 178)	168 (50 – 182)	168 (43 – 182)	168 (122 – 178)
Total exposure (person years)**	13.125	13.993	13.457	12.775
Cumulative duration of exposure 20-24 weeks, n (%)	28 (96.6)	30 (96.8)	28 (93.3)	27 (96.4)

Drug exposure was calculated over the interval for which study drug dispense and return data are available.
* Duration of exposure (days) = (date of last dose of study medication – date of first dose of study medication) + 1
** Person year = (sum of duration of exposure to treatment (days) over all patients) / 365.25
Abbreviations: Kg – Kilogram; Mg – Milligram.
Source: VISION-DMD CSR[6]

B.2.10.1.2. Treatment-emergent adverse events

A summary of treatment-emergent adverse events (TEAEs) reported in patients during period 1 (24-weeks) are shown in Table 33. Details on how these have been included within the cost-effectiveness model (CEM) are presented in Section B.3.4. Measurement and valuation of health effects

During the 24-week period, the overall incidence of TEAEs was similar in the vamorolone 6.0 mg/kg/day and the prednisone group. TEAEs were reported in 25 out of 30 (83.3%) patients who received vamorolone 2.0 mg/kg/day and 25 out of 28 (89.3%) who received vamorolone 6.0 mg/kg/day compared to 26 patients (83.9%) receiving prednisone and 23 patients (79.3%) receiving placebo (Table 33).[4]

Drug-related TEAEs were most commonly reported in patients receiving vamorolone 6.0 mg/kg/day (67.9%), followed by those receiving prednisone (45.2%), yet only 33.3% of patients in the vamorolone 2.0 mg/kg/day group experienced these.[6] In patients receiving vamorolone, all TEAEs were mild to moderate however severe TEAEs were reported by one patient (3.2%) treated with prednisone. While TEAEs leading to dose interruption were reported in one (3.6%) and two (6.7%) patients in the vamorolone 6.0 mg/kg/day and 2.0 mg/kg/day arms, respectively, no TEAEs led to treatment withdrawal in either

group. Conversely, one patient (3.2%) receiving prednisone reported a TEAE leading to dose interruption which consequently led to treatment withdrawal and eventual study withdrawal. The patient had a Grade 2 TEAE of personality change with onset on Day 43, leading to dose-tapering on Day 44, and study discontinuation on Day 72. The TEAE resolved on Day 72 and was assessed by the investigator as possibly related to the prednisone drug. Such discontinuation and withdrawal from treatment is a detrimental but common problem seen with steroid treatments which has not been seen to occur in vamorolone patients, demonstrating the milder TEAE profile with vamorolone and suggesting greater adherence potential.

No TEAEs leading to death were reported across any treatment arm.[6]

This evidence the absence of any negative effects on growth seen with vamorolone compared to prednisone. Additional TEAEs reported in the VISION-DMD study include adrenal suppression, growth stunting and bone health. Treatment with vamorolone 2.0 and 6.0 mg/kg/day led to dose-dependent adrenal suppression.[6] The degree of adrenal suppression was similar in vamorolone 6.0 mg/kg/day and prednisone, while it was less pronounced in vamorolone 2.0 mg/kg/day. Growth stunting was also seen with prednisone during the first 24 weeks of treatment, but it was not seen with vamorolone. Additionally, this stunting of growth seen with prednisone was rescued following the switch to either vamorolone 2.0 or 6.0 mg/kg/day in the subsequent 24-48 week period of evaluation.[6] This evidences the absence of any negative effects on growth seen with vamorolone compared to prednisone. This supports the improved safety profile of vamorolone on bone health, as no biomarkers showed mean declines in either vamorolone dose group.[6] Instead, mean changes from baseline to Week 24 for a range of bone biomarkers (osteocalcin, P1NP, and s-CTX) were maintained or improved in both vamorolone groups. Contrastingly, significant reductions from baseline to Week 24 were seen in all bone biomarkers after treatment with prednisone. No treatment-emergent vertebral fractures were seen in either of the vamorolone groups at Week 24, but were seen in one subject in the placebo group and one subject in the prednisone group.[6]

Table 33: Summary of TEAEs at 24 weeks

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
TEAEs (%)	23 (79.3)	26 (83.9)	25 (83.3)	25 (89.3)
Drug-related TEAEs (%)	8 (27.6)	14 (45.2)	10 (33.3)	19 (67.9)
Severe TEAEs (%)	0	1 (3.2)	0	0
Serious TEAEs (%)	0	0	1 (3.3)	0
TEAEs leading to dose interruption (%)	0	1 (3.2)	2 (6.7)	1 (3.6)
TEAEs leading to withdrawal from treatment (%)	0	1 (3.2)	0	0
TEAEs leading to withdrawal from study (%)	0	1 (3.2)	0	0
TEAEs leading to death (%)	0	0	0	0

Abbreviations: Kg – Kilogram; Mg – Milligram; TEAE - treatment-emergent adverse events.
Source: VISION-DMD CSR[6]

B.2.10.1.3. Clinically relevant AEs

Clinically relevant AEs were AEs that met one of the following criteria: 1) grade 2 or higher in severity; 2) was serious; or 3) led to premature discontinuation of study treatment. Overall, clinically relevant AEs were reported in 41.9% of patients in the prednisone group, compared to a much lower percentage of patients in the vamorolone 2.0 mg/kg/day (26.7%) and 6.0 mg/kg/day groups (14.3%) (Table 34).[6] No significant difference was seen across the groups in the time between study entry and a clinically relevant AE.

Clinically relevant AEs that were reported in a higher percentage of patients in the prednisone group compared with either of the vamorolone groups included psychiatric disorders.[6] The higher incidence of clinically relevant psychiatric AEs in the prednisone group (19.4% compared to 0% in either vamorolone group) occurred due to a number of individual AEs including aggression (two patients) and emotional disorders, mood swings, personality change, sleep disorder, and trichotillomania (one patient each).

Table 34: Clinically relevant AEs

Clinically Relevant AEs System Organ Class	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
At least 1 clinically relevant TEAE	9 (31.0)	13 (41.9)	8 (26.7)	4 (14.3)
Endocrine disorders	0	0	0	1 (3.6)
Hepatobiliary disorders	0	0	0	1 (3.6)
Injury, poisoning and procedural complications	1 (3.4)	1 (3.2)	3 (10.0)	1 (3.6)
Metabolism and nutrition disorders	0	1 (3.2)	1 (3.3)	1 (3.6)
Musculoskeletal and connective tissue disorders	0	0	1 (3.3)	1 (3.6)
Renal and urinary disorders	0	0	0	1 (3.6)
Gastrointestinal disorders	1 (3.4)	1 (3.2)	1 (3.3)	0
General disorders and administration site conditions	1 (3.4)	0	0	0
Infections and infestations	3 (10.3)	4 (12.9)	2 (6.7)	0
Investigations	0	2 (6.5)	1 (3.3)	0
Nervous system disorders	1 (3.4)	1 (3.2)	0	0
Psychiatric disorders	1 (3.4)	6 (19.4)	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (3.2)	0	0
Skin and subcutaneous tissue disorders	1 (3.4)	0	0	0

TEAEs are defined as any adverse event starting or worsening after initiation of the investigational product and through the subject's last study visit (study completion or early termination).
Serious AEs (SAEs) were recorded for up to 30 days after the final administration of study drug
For the period #1 analyses, AEs, SAEs and TEAEs with onset through the subject's Week 24 F/U Visit are included. Table is sorted in descending order of SOCs and PTs in the Vamorolone 6.0 treatment group
This table includes TEAEs that meet any of the following criteria: Severity of grade 2 and higher or TEAE leading to premature discontinuation of study treatment or Serious TEAE
Abbreviations: AE – Adverse event; Kg – Kilogram; Mg – Milligram; TEAE – Treatment-emergent adverse event.
Source: VISION-DMD CSR[6]

B.2.10.1.4. Most common TEAEs

Common TEAEs were considered to be those present in ≥3 patients or >10% of the entire study population across all groups and are shown in Table 35. The sum of all the TEAEs experienced in both vamorolone groups was 37,

compared to 50 TEAEs seen in the prednisone group, suggesting vamorolone was better tolerated than prednisone at both dosages.[6]

Cushingoid features were the most common TEAE in both the vamorolone 6.0 mg/kg/day group (28.6%) and prednisone group (22.6%), while the vamorolone 2.0 mg/kg/day group (6.7%) incidence was significantly lower.[6] Total upper respiratory tract infections were the second most reported TEAE across all groups, yet this was reported in just 7.1% of patients receiving vamorolone 6.0 mg/kg/day compared to almost double that (12.9% of patients) in the prednisone arm.

Abdominal pain was also more common in prednisone patients (9.7%) compared with the vamorolone 6.0 mg/kg/day group (7.1%) and equivalent to vamorolone 2.0 mg/kg/day (10%), yet upper abdominal pain was greater in the prednisone group (9.7%) compared to either vamorolone group (7.1% and 0% respectively).[6] Similarly, the incidence of nasopharyngitis and rashes in the prednisone group were both 9.7%, higher than those in the vamorolone 6.0 mg/kg/day condition (7.1% for both TEAEs) and the vamorolone 2.0 mg/kg/day condition (3.3% and 0% respectively). Extremity pain TEAEs were also more common in prednisone patients (9.7%), with none being reported in either vamorolone groups. Falls, coughs and weight gain TEAEs in the prednisone group were also either similar to or lower than prednisone in both vamorolone groups. Both vamorolone conditions therefore do not worsen the pain or discomfort experienced by patients during these AEs when compared to prednisone.

Table 35: Most common TEAEs at 24-weeks

TEAE	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Cushingoid	0	7 (22.6)	2 (6.7)	8 (28.6)
Upper respiratory tract infection	4 (13.8)	4 (12.9)	6 (20.0)	2 (7.1)
Pyrexia	6 (20.7)	2 (6.5)	6 (20.0)	0
Vomiting	2 (6.9)	2 (6.5)	5 (16.7)	4 (14.3)
Abdominal pain upper	1 (3.4)	3 (9.7)	0	2 (7.1)
Abdominal pain	2 (6.9)	3 (9.7)	3 (10.0)	2 (7.1)
Cough	1 (3.4)	3 (9.7)	3 (10.0)	2 (7.1)
Nasopharyngitis	3 (10.3)	3 (9.7)	1 (3.3)	2 (7.1)
Fall	1 (3.4)	4 (12.9)	0	3 (10.7)
Rash	3 (10.3)	3 (9.7)	0	2 (7.1)
Constipation	2 (6.9)	1 (3.2)	3 (10.0)	1 (3.6)
Irritability	0	1 (3.2)	0	3 (10.7)
Vitamin D deficiency	0	1 (3.2)	2 (6.7)	3 (10.7)
Weight increased	1 (3.4)	2 (6.5)	0	3 (10.7)
Protein urine present	0	4 (12.9)	1 (3.3)	0
Psychomotor hyperactivity	0	3 (9.7)	2 (6.7)	0
Contusion	0	1 (3.2)	3 (10.0)	0
Pain in extremity	1 (3.4)	3 (9.7)	0	0

(TEAEs are defined as any adverse event starting or worsening after initiation of the investigational product and through to the patient's last study visit (study completion or early termination).
AEs, SAEs and TEAEs with onset through the patient's Week 24 follow-up visit are included.
Abbreviations: AE – Adverse event; Kg – Kilogram; Mg – Milligram; SAE – Serious adverse event; TEAE – Treatment-emergent adverse event.
Source: VISION-DMD CSR[6]

B.2.10.1.5. Adverse events of special interest

Adverse events of special interest (AESI) were defined based on the safety profile known for glucocorticoids and are summarised in Table 36. There was no evidence of an increased risk for infections, hypertension, diabetes, cataracts/glaucoma, skin disorders, or hirsutism with vamorolone.[6] No significant difference was seen across the groups in the time to an AESI during the 24-week period. Reported TEAE's of special interest totalled 61 in the prednisone group and 42 for each vamorolone arm. The most common AESIs were similar in each group and comprised behavioural problems, cushingoid features and infections.

Behavioural problems were reported in five (16.7%) and six (21.4%) patients in the vamorolone 2.0 and 6.0 mg/kg/day group respectively, almost half those reported in the prednisone group (10 patients, 32.3%) (Table 36).[6] Given the higher incidence of behavioural problems in DMD patients undergoing corticosteroid treatment, minimising the additional risk of developing treatment-related behavioural problems is a benefit of vamorolone. The most common behavioural problems experienced were similar between both vamorolone groups and prednisone, but the severity of the behavioural problems in the prednisone group was higher than in the vamorolone and placebo groups. One patient in the prednisone group discontinued the study because of personality change. Similar values were seen for the vamorolone groups compared with the placebo and prednisone groups in either PARS III total score or the sub-scores for peer relations, dependency, anxiety, depression, and withdrawal at Week 24, evidencing that vamorolone does not have any greater detrimental impact on patient mental wellbeing when compared to prednisone.

Cushingoid features were reported in a lower percentage of the vamorolone 2.0 mg/kg/day group (6.7%) compared to the prednisone (22.6%) and vamorolone 6.0 mg/kg/day (28.6%) groups.[6] All TEAEs of cushingoid features were mild to moderate, and no patient interrupted or discontinued vamorolone due to this TEAE. This demonstrates that prednisone treatment provides a similar or greater risk of cushingoid feature TEAEs compared against vamorolone 2.0 mg/kg/day, and the consequential impact on patient confidence, mental wellbeing, and social interaction. Additionally, only one subject in vamorolone 6.0 mg/kg/day reported cushingoid features in Period 2, compared to eight subjects in Period 1; this indicates a lower incidence of developing cushingoid features after the first six months of therapy at this dose.

Infections were common across all four treatment arms with the highest rate seen in the placebo group (44.8%). Infection TEAEs were not directly associated with treatment, given lower incidences were seen in both vamorolone 6.0 mg/kg/day (32.1%) and prednisone (38.7%).[6]

AEs of weight gain were reported in a similar percentage of patients in the vamorolone 2.0 mg/kg/day group (3.3%) compared with the placebo group (6.9%) and a higher percentage of patients in the prednisone group (9.7%).[6] AEs of weight gain were reported in a similar number of patients in the vamorolone 6.0 mg/kg/day group (five patients) compared with the prednisone group (three patients),similar mean and median increases in weight, weight percentile, and weight Z-score in these groups.

Diabetic conditions were based on AEs of symptoms and signs that can be associated with the development of diabetes mellitus and diabetes-related laboratory values (i.e., fasting insulin, fasting glucose, and HbA1c levels, triglyceride levels).[6] A lower percentage of patients in the vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day groups (0% and 3.6% respectively), and placebo (3.4%) group, compared with the prednisone (9.7%) group had an AE that could be associated with diabetes mellitus.

Table 36: Adverse events of special interest

	Placebo (n=29)	**Prednisone (n=31)**	**Vamorolone 2.0 mg/kg/day (n=30)**	**Vamorolone 6.0 mg/kg/day (n=28)**
At least 1 clinically relevant AE	9 (31.0)	13 (41.9)	8 (26.7)	4 (14.3)
Behaviour problems	4 (13.8)	10 (32.3)	5 (16.7)	6 (21.4)
Cataracts and glaucoma	0	0	0	0
Cushingoid features	0	7 (22.6)	2 (6.7)	8 (28.6)
Gastrointestinal symptoms	8 (27.6)	8 (25.8)	9 (30.0)	8 (28.6)
Hypertension	0	1 (3.2)	1 (3.3)	0
Infections	13 (44.8)	12 (38.7)	13 (43.3)	9 (32.1)
Adrenal disorder	0	0	0	0
Diabetic conditions	1 (3.4)	3 (9.7)	0	1 (3.6)
Skin/hair changes	2 (6.9)	4 (12.9)	3 (10.0)	1 (3.6)
Weight gain	2 (6.9)	3 (9.7)	1 (3.3)	5 (17.9)

Abbreviations: AE – Adverse event; Kg – Kilogram; Mg – Milligram.
Source: VISION-DMD CSR[6]

B.2.10.2. Week 48 results, VISION-DMD

After 48 weeks of treatment, no deaths were reported during the study. Three serious AEs were reported, which included: perforated appendicitis

(vamorolone 6.0 mg/kg/day), asthma (vamorolone 6.0 mg/kg/day), and viral gastroenteritis (vamorolone 2.0 mg/kg/day), all considered unrelated to vamorolone.[5] The most common AEs reported during 48 weeks of vamorolone treatment are shown in Table 37. The percentage of patients with at least one drug-related AE decreased in both vamorolone groups in period 2 relative to period 1 and continued to be lower in the vamorolone 2.0 mg/kg/day group compared with the 6.0 mg/kg/day group in period 2 (17.9% vs. 39.3%, respectively).

Table 37: Common AEs for vamorolone

	Vamorolone 2.0 mg/kg/day	**Vamorolone 6.0 mg/kg/day**
Upper respiratory tract infections, n (%)	10 (35.7)	4 (14.3)
Vomiting, n (%)	6 (21.4)	6 (21.4)
Cushingoid features, n (%)	4 (14.3)	9 (32.1)
Cough, n (%)	5 (17.9)	3 (10.7)
Pyrexia, n (%)	7 (25.0)	3 (10.7)
Diarrhoea, n (%)	3 (10.7)	5 (17.5)

Abbreviations: AE – Adverse event; Kg – Kilogram; Mg – Milligram.
Source: Hoffman et al. 2023[5]

B.2.10.2.1. AEs in switching from prednisone to vamorolone

The overall incidence of AEs decreased after the switch from prednisone to vamorolone in period 2. Fewer AESIs were recorded in period 2 compared to period 1.[5] No SAEs were reported after the switching from prednisone to either vamorolone dose. Following the switch from prednisone (period 1) to vamorolone (period 2), annualised rates of AEs (AEs/patient/year) were reduced (all events: 19.3% reduction; AESIs: 39.7% reduction). Out of all AESIs, the largest reductions in annualised rates of AEs/patient/year were seen in:[5]

- Behaviour problems (prednisone versus vamorolone: 1.08 to 0.51 [52.8% change])
- Gastrointestinal symptoms (prednisone versus vamorolone: 0.72 to 0.60 [16.7% change])
- Cushingoid features, as a lower incidence of developing cushingoid features was noted after the first 6 months of therapy at 6.0 mg/kg/day (one patient in period 2 compared to eight in period 1)

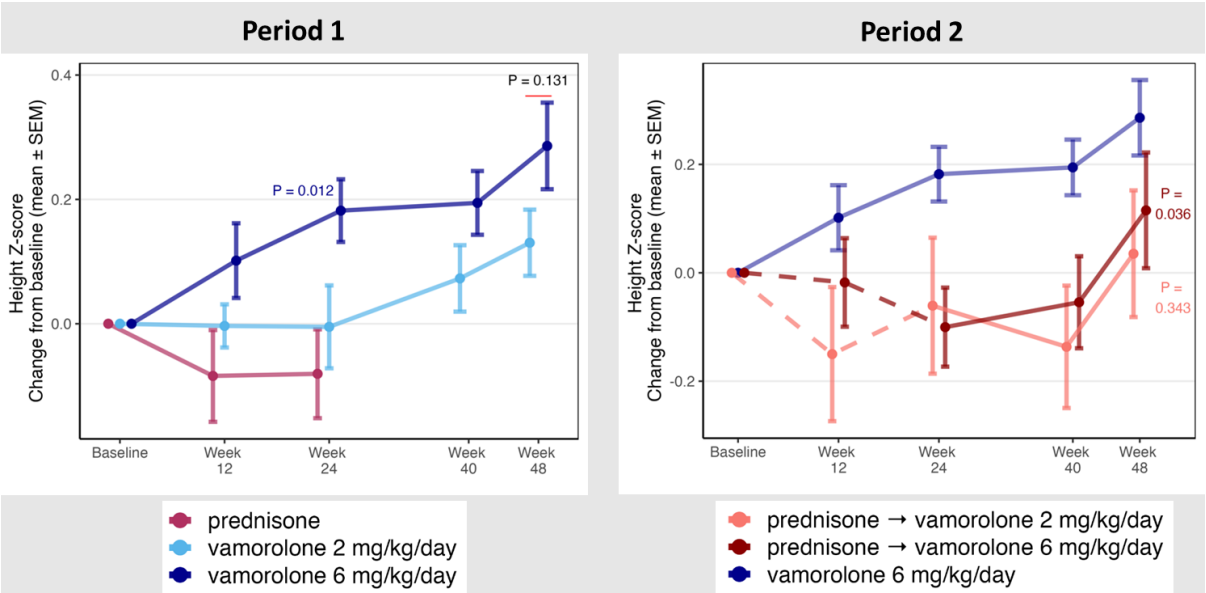
- Cushingoid features were not reported in participants switching from prednisone to vamorolone 2.0 mg/kg/day and only one patient-reported the onset of cushingoid features after switching from prednisone to vamorolone 6.0 mg/kg/day

- Weight gain, where a low incidence was observed for weight gain in period 2 (only in one participant on vamorolone 2.0 mg/kg/day) as well as in those who crossed over to vamorolone

B.2.10.2.2. Growth and bone-related outcomes

Treatment with vamorolone for 48 weeks resulted in normal growth trajectories in participants, with no significant dose-dependent differences (vamorolone 6.0 mg/kg/day versus vamorolone 2.0 mg/kg/day: p=0.131).[5] In the prednisone to vamorolone crossover participants, prednisone showed slowing of growth velocities in period 1, and after crossover to vamorolone 6.0 mg/kg/day showed reversal of growth trajectories (height Z-score) via catch-up growth (period 1 LSM: -0.10; period 2 LSM: 0.13; LSM [CI]: 0.23 [0.02, 0.44]; p=0.036). Comparing prednisone crossover to vamorolone 6.0 mg/kg/day to those on vamorolone 6.0 mg/kg/day throughout the 48-week treatment period shows catch-up growth, with lower height at Week 48 assessment for those initially treated with prednisone (LS mean [CI]: 0.07 [-0.15, 0.28]; p=0.53), as presented in Figure 20.

Figure 20: Height Z-score changes from period 1 prednisone switch to vamorolone



Abbreviations: Kg – Kilogram; Mg – Milligram; SEM – Standard error of the mean.

Source: Hoffman et al. 2023[5]

Although the first 24 weeks of treatment with vamorolone was associated with a smaller percent increase in lumbar spine bone mineral content (BMC) bone mineral density (BMD) compared to placebo, this recovered between Week 24 and Week 48, reaching percent change increases similar to that observed on placebo in the first 24 weeks.[6] Of note, placebo patients who switched to vamorolone in Period 2 showed a similar pattern as observed in patients starting on vamorolone in Period 1; it is not clear if this small effect could be related to the catch-up growth observed in some patients during that period.

In contrast, prednisone treatment was associated with an approximately 50% reduction of the median percent increase BMC and a small negative median percent change BMD over 24 weeks, suggesting a negative effect on bone architecture.[6] The percent change in BMC and BMD over 24 weeks clearly improved in prednisone treated patients after switching to vamorolone, also becoming similar to the placebo rates observed in Period 1.

The observed differential effect of prednisone compared to vamorolone on BMC and BMD over the first 24 weeks and the recovery to placebo-like values after switching to vamorolone is consistent with the results observed in the bone biomarkers. These results further support that vamorolone has a differential effect on bone health compared to prednisone.

B.2.10.2.3. Changes in body mass index

BMI increased over 24 weeks of treatment in period 1 for both vamorolone dose groups and those on prednisone, then BMI stabilised for period 2.[5] In the prednisone to vamorolone crossover groups, the weight gain seen with prednisone in period 1 stabilised with crossover to the 6.0 mg/kg/day vamorolone in period 2. Prednisone to 2.0 mg/kg/day vamorolone showed a reduction in BMI towards baseline although the difference between these two groups was not statistically significant (LS mean [CI]: 0.18 [-0.11, 0.47]; p=0.21).

B.2.10.2.4. Biomarkers

The decrease in serum bone turnover markers (osteocalcin, PINP, CTX) seen in the prednisone group during period 1 was quickly reversed after tapering prednisone and then switching to vamorolone during period 2.[5] Furthermore, all the treatment groups except placebo showed evidence of adrenal suppression measured by both morning cortisol and ACTH-stimulated tests after 24 weeks of treatment. After 48 weeks of treatment, the degree of adrenal suppression was stable compared to Week 24 assessment.

B.2.10.3. VBP15-LTE

Of patients treated with 6.0 mg/kg/day, 10 patients (24.4%) deescalated to 2.0 mg/kg/day owing to a treatment-emergent AE of weight gain.[68] The AE abated among six participants after dose reduction.

Among the 46 extended study participants, six participants (13.0%) were observed to have a total of seven clinical fracture events according to local site adverse event reporting, including one participant with a vertebral fracture and a foot fracture on two separate occasions, three participants with an upper limb fracture, one participant with a vertebral compression fracture, and one participant with multiple vertebral fractures. There were two serious TEAEs: moderate pneumonia in one participant and severe myoglobinuria, which occurred twice in one participant. One participant withdrew from the study due to moderate muscle weakness. The investigators considered that the TEAEs were not associated with vamorolone.

A summary of TEAEs is presented in Table 38.

Table 38: Summary of TEAEs, VBP15-LTE

	0.25 mg/kg/day (n=11)	0.75 mg/kg/day (n=23)	2.0 mg/kg/day (n=38)	4.0 mg/kg/day (n=3)	6.0 mg/kg/day (n=41)
Any TEAE, n (%)	4 (36.4)	14 (60.9)	29 (76.3)	1 (33.3)	39 (95.1)
Any Treatment-related TEAE	0	0	8 (21.1)	1 (33.3)	23 (56.1)
Any TEAE with CTCAE Grade ≥ 3	0	1 (4.3)	0	0	1 (2.4)
Any TEAE Leading to Discontinuation of Study	0	0	1 (2.6)	0	0
Any SAE	0	1 (4.3)	0	0	1 (2.4)
Any Serious TEAE	0	1 (4.3)	0	0	1 (2.4)

Abbreviations: CTCAE – Common Terminology Criteria for AEs; Kg – Kilogram; Mg – Milligram; SAE – Serious adverse event; TEAE – Treatment-emergent adverse event.
Source: Mah et al. 2022[68]

B.2.10.4. Safety conclusions

The overall incidence of TEAEs in vamorolone studies was similar across treatment arms, however when considering clinically relevant TEAEs, incidence in the vamorolone groups was lower than in the prednisone group. 6.0 mg/kg/day of vamorolone did not demonstrate any reduction in safety or tolerability compared to 2.0 mg/kg/day. In the VISION-DMD study, while TEAEs leading to dose interruption were reported in one (3.6%) and two (6.7%) patients in the vamorolone 6.0 mg/kg/day and 2.0 mg/kg/day arms respectively, no TEAEs led to treatment withdrawal in either group[4]. Conversely, one patient (3.2%) receiving prednisone reported a TEAE leading to dose interruption which consequently led to treatment withdrawal and eventual study withdrawal. In addition, mean and median changes from baseline to Week 24 for osteocalcin, P1NP, and s-CTX were small and similar in the vamorolone 2.0 mg/kg and 6.0 mg/kg groups. In contrast, significant reductions from baseline to Week 24 were seen in all bone biomarkers for the prednisone group.

After 48 weeks of treatment, no deaths were reported during the study. Three serious AEs were reported, which included: perforated appendicitis (vamorolone 6.0 mg/kg/day), asthma (vamorolone 6.0 mg/kg/day), and viral gastroenteritis (vamorolone 2.0 mg/kg/day) all considered unrelated to vamorolone. The most common AEs reported during 48 weeks of vamorolone treatment were: upper respiratory tract infections, vomiting, cushingoid features, cough, pyrexia and diarrhoea (Table 37).

Importantly, following the switch from prednisone (period 1) to vamorolone (period 2), annualised rates of AEs (AEs/patient/year) were reduced.[5] Furthermore, while treatment with vamorolone for 48 weeks showed normal growth trajectories in participants, with no significant dose-dependent differences, in the prednisone to vamorolone crossover participants, vamorolone 6.0 mg/kg/day showed reversal of growth trajectories via catch-up growth.

The results of the VISION-DMD study were consistent with those reported in the preceding Phase II studies, particularly the VBP15-003 study which demonstrated the reduction in AEs typically seen in DMD patients treated with glucocorticoids and the VBP15-LTE study which showed long-term vamorolone treatment at doses up to 6.0 mg/kg/day were well-tolerated.[4,67,68]

B.2.11. Ongoing studies

There is currently an EAP ongoing. Subjects with DMD who completed the clinical trials VBP15-LTE (NCT03038399) and VISION-DMD (NCT03439670) were offered access to continue treatment with vamorolone 2-6 mg/kg in an EAP, which was individualized for the participating countries. Subjects participating in Canada, United States (US) and Israel entered under an EAP for their country. Subjects participating in other countries, including European countries and Australia, are being treated in the context of different compassionate use (or named patient mechanism) programs (CUP) adjusted to the regulations in their respective countries.

In the EAP, patients receive standard of care as recommended by their treating physician. Treating physicians participating in the EAP are required to collect and document any physician, patient, or caregiver reported safety events and report to the sponsor. Doses of vamorolone can be increased or decreased within a range of 2.0 to 6.0 mg/kg/day (with exact dosing restricted to 2.0 mg/kg/day, 4.0 mg/kg/day and 6.0 mg/kg/day only).[87]

VBP15-006 is an ongoing, Phase II, open-label, multiple dose study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behaviour and

neuropsychology, and physical functioning of vamorolone in DMD.[88] VBP15-006 is investigating vamorolone administered orally at 2.0 mg/kg/day and 6.0 mg/kg/day over a treatment period of 3 months in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

B.2.12. Interpretation of clinical effectiveness and safety evidence

The efficacy, safety, PD, and PK of vamorolone was assessed across a number of clinical studies. The pivotal VISION-DMD study was a Phase IIb randomised, double-blind, parallel-group study, conducted in collaboration with the CINRG and included ambulatory boys with DMD who were corticosteroid-naïve at study entry.[4]

The primary efficacy endpoint, TTSTAND velocity, was significantly improved with vamorolone 6.0 mg/kg/day compared with placebo at week 24.[4] This is of relevance as the improvement also demonstrated a clinically important difference and is predictive of a delay of 2-3 years until loss of ambulation.[69] In addition, significant and clinically meaningful (i.e., >30 metres) improvements in 6MWT distance were demonstrated with vamorolone 6.0 mg/kg/day versus placebo at Week 24.[4] Vamorolone also demonstrated significant improvements versus placebo in other secondary endpoints including TTRW velocity, TTCLIMB velocity and NSAA score.[4] These results were also seen with sensitivity analyses as well as subgroup analyses which demonstrate the consistency of results for vamorolone.[4] The improvements versus placebo observed at 24 weeks in the vamorolone 6.0 mg/kg/day group were maintained in all five endpoints (TTSTAND velocity, 6MWT distance, TTRW velocity, NSAA, TTCLIMB velocity) to period 2 (48 weeks).[5] Treatment with vamorolone 2.0 mg/kg/day, for 48 weeks showed a reduction of the improvements that were seen at the Week 24 assessment towards baseline function for TTSTAND velocity and 6MWT distance, but stabilisation of improved function relative to baseline for TTRW velocity, NSAA and TTCLIMB velocity.[5] For patients who

crossed over from prednisone to vamorolone 6.0 mg/kg/day treatment, maintenance of benefit for TTSTAND, 6MWD and NSAA was shown.[5]

While height percentile declined in patients treated with prednisone, this was not seen in vamorolone-treated patients. Furthermore, after 48 weeks of treatment normal growth trajectories were maintained in patients receiving vamorolone, with no significant dose-dependent differences.[5] In the prednisone to vamorolone crossover patients, vamorolone 6.0 mg/kg/day showed reversal of growth trajectories via catch-up growth.[5] This is supported by the post-hoc indirect comparison which also showed improvement in height z-scores for patients treated with vamorolone compared to those treated with prednisone and deflazacort.[76]

Patient bone health was also maintained to a greater extent in vamorolone patients compared to prednisone.[4] Mean changes from baseline to Week 24 for a range of bone biomarkers (osteocalcin, P1NP, and s-CTX) were improved in both vamorolone groups. Contrastingly, significant reductions from baseline to Week 24 were seen in all bone biomarkers after treatment with prednisone. This decrease in bone biomarkers seen in the prednisone group during period 1 was quickly reversed after tapering prednisone and then switching to vamorolone during period 2.[5]

The overall incidence of TEAEs was comparable in the vamorolone 6.0 mg/kg/day group and the prednisone group.[4] Except for a severe AE of aggression in the prednisone group, all TEAEs reported in the 24-week period were mild to moderate. Cushingoid features were the most common TEAE and were reported in a higher proportion of patients with vamorolone 2.0 mg/kg/day and vamorolone 6.0 mg/kg/day than with placebo. Notably, only one subject in vamorolone 6.0 mg/kg/day reported cushingoid features in Period 2, compared to eight subjects in Period 1, suggesting a lower incidence of developing cushingoid features after the first six months of therapy at this dose.[5] Behavioural problems were another common AESI given the increased prevalence of behavioural issues in DMD patients and were reported in almost double the number of patients in the prednisone group than either of the

vamorolone groups. No deaths or SAEs related to study drug were reported during the study, whereas one patient in the prednisone group was required to have their dosing tapered and ultimately withdraw from the study due to adverse behavioural effects. These side effects are a primary reason for patient refusal or non-adherence to traditional corticosteroid treatments and are minimised with vamorolone.

Results from the VISION-DMD study were consistent with those reported in the three preceding Phase II studies. After 30-months of treatment, vamorolone showed similar treatment efficacy as glucocorticoids in DMD, and the decline was slower compared with that of untreated patients.[68] Patients receiving higher doses also had persistent improvement in motor function as measured by TTCLIMB, TTRW, NSAA and 6MWT. Importantly, long-term vamorolone doses were safe and well-tolerated, showing a reduction in AEs typically seen in DMD patients treated with long-term glucocorticoids.

In conclusion, vamorolone is a safe, effective, and well-tolerated treatment that has been shown to improve motor function compared with placebo and has demonstrated equivalent efficacy to glucocorticoids. The efficacy of vamorolone is equivalent to that of glucocorticoids, with its additional benefit seen in terms of reduced AE's. Vamorolone avoids several of the AEs associated with glucocorticoids, resulting in a favourable bone biomarker profile, no stunting of growth and fewer vertebral fractures (these fractures are predictive of future fractures). An improved safety profile also encourages patients to remain on-treatment and consequently receive the full beneficial effects of vamorolone.

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

An economic SLR was conducted to identify economic evidence for vamorolone and other interventions for the treatment of boys with DMD. The SLR was originally conducted in 2017, with an update in 2019 and further updated in July 2023 for the purposes of this submission. The methodology undertaken is summarised in Appendix G, which details the search strategy, eligibility criteria applied, and full list of included references. The key objective of the SLR was to identify cost-effectiveness studies of therapies available for the treatment of DMD. The review question that was used to identify the studies was:

- What cost-effectiveness analysis evidence is available for the treatment of DMD?

The economic SLR update identified one relevant published source; five studies were identified in the previous SLRs A summary of the sources and data extracted are presented in Table 39 below.

Table 39: Summary 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)
Landfeldt 2017[89]	2015	Objective was 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. The base case perspective was a UK healthcare perspective. Additional SA analysed a wider UK societal perspective. Three cost-effectiveness Markov models were used: Model I used 25 health states based upon DMDSAT score (DMDSAT score: 23; DMDSAT score: 22; DMDSAT score: 21; DMDSAT score: 0; and dead). 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). Model III used 4 health states based on ventilation status (no ventilation support; night-time ventilation support; night- and daytime ventilation support; and dead). In all models, a lifetime horizon was used (until natural death or until aged 100) and Cycle length was 12 months. Patient utilities were derived using HUI. Caregiver utilities were assessed by EQ-	5 (hypothetical cohort)	**Treatment** Model I: Patients 8.13 Caregivers 12.93 Model II: Patients 7.96 Caregivers 12.89 Model III: Patients 6.93 Caregivers 12.72 **Standard of care** Model I: Patients 7.07 Caregivers 12.80 Model II: Patients 7.17 Caregivers 12.82 Model III: Patients 5.96 Caregivers 12.66	**Treatment** Model I: Healthcare £1,737,960 Societal £2,117,140 Model II: Healthcare £1,768,370 Societal £2,171,380 Model III: Healthcare £1,809,160 Societal £2,232,890 **Standard of care** Model I: Healthcare £217,510 Societal £624,240 Model II: Healthcare £244,120 Societal £663,500 Model III: Healthcare £284,640 Societal £713,840	All results are ICERs per QALY for a hypothetical treatment for DMD vs. standard of care. **Base case** Model I: Healthcare £1,442,710 Societal £1,266,510 Model II: Healthcare £1,939,590 Societal £1,760,650 Model III: Healthcare £3,574,770 Societal £3,121,890 **Scenario analyses ICER range:** Model I: £1,324,740 - £3,313,550

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency, intervention, comparator)	ICER (per QALY gained)
		5D-3L. Utilities were estimated from a previous cross-sectional, observational study. 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).[58] Model III derived state transition probabilities from the mean time to ventilation support based on clinical experience and published evidence. In all models it was assumed that patients enter in the least bad state (DMDSAT 23; early ambulatory; no ventilation support). 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.[31,46] Data for mortality for patients younger than 18 was taken from age-specific UK				Model II: £1,479,360-£2,131.650 Model III: £2,394,430-£4,064,600

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency, intervention, comparator)	ICER (per QALY gained)
		male general population mortality rates from UK Office for National Statistics (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. Costs and QALYs were discounted at 3.5% per annum.				
NICE 2015a	2014	The objective was to perform a cost-consequence analysis of Translarna (ataluren) on a platform of BSC compared to BSC alone for the treatment of DMD in ambulatory patients aged ≥5 years. The perspective was the UK NHS and PSS. Cost-effectiveness semi-Markov model with six mutually exclusive health states (ambulatory; non- ambulatory; non-ambulatory ventilation assisted; non-ambulatory scoliosis; non ambulatory with scoliosis and ventilation assisted; and dead). Time horizon was for the duration of treatment (while in ambulatory state) with 3- monthly Cycles. Efficacy data was extrapolated from a 48-week clinical trial and time to states was taken from published literature. Direct and indirect health state costs	8.5	**Ataluren** Ambulatory 6.506 Non-ambulatory 0.006 Non-ambulatory and ventilation assisted 0.000 Non ambulatory with scoliosis -0.120 Non-ambulatory with scoliosis and ventilation assisted -0.240 **Total** 6.152 **BSC** Ambulatory 3.006 Non-ambulatory	**Ataluren** Ambulatory £4,984,263 Non-ambulatory £9,774 Non-ambulatory and ventilation assisted £521 Non ambulatory with scoliosis £37,961 Non-ambulatory with scoliosis and ventilation assisted £60,021 **Total** £5,092,540 **BSC** Ambulatory £29,752 Non-ambulatory	Not reported

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency, intervention, comparator)	ICER (per QALY gained)
		were taken from a study by Landfeldt (Landfeldt et al 2014), ONS and OECD. NHS reference costs were used for surgery & surgery follow-up costs. Utilities for both patients and caregivers were taken from Landfeldt et al 2014. Costs and benefits were discounted at 3.5% per annum.		0.022 Non-ambulatory and ventilation assisted 0.000 Non ambulatory with scoliosis -0.343 Non-ambulatory with scoliosis and ventilation assisted -0.300 **Total** 2.385	£34,657 Non-ambulatory and ventilation assisted £520 Non ambulatory with scoliosis £96,964 Non-ambulatory with scoliosis and ventilation assisted £73,314 **Total** £235,207	
SMC 2016	Not stated	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. A multi-state semi-Markov model was used with 6 health states (ambulatory; non-ambulatory; non-ambulatory ventilation assisted; non-ambulatory scoliosis; non ambulatory with scoliosis and ventilation assisted; and dead). The time horizon and Cycle length used in the model are not stated. Clinical data was sourced from a clinical trial and extrapolated (study ID PTC124-GD-007-DMD).[90] Published sources were used to estimate time to loss of ambulation curves, transition probabilities from	8.5	**Base case** Incremental QALY for Ataluren vs. BSC 6.089	**Base case** Incremental cost for Ataluren vs. BSC £4,891,213	**Base case** £793,498/ QALY for Ataluren vs. BSC

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency, intervention, comparator)	ICER (per QALY gained)
		non-ambulatory health state to ventilation assistance and/or scoliosis health states for the comparator, and the transition to the death health state for BSC. 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. 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. Discounting was increased to 6% per annum in sensitivity analysis but the base case was not stated.				
Magnetta 2016	Not stated	Objective was to evaluate the cost-effectiveness of continuous flow VAD destination therapy compared to MM in DMD with advanced heart failure. Cost-effectiveness Markov- state transition model to compare survival, costs, and QoL between MM and VAD therapy for DMD patients. Health states for the model were not stated. 5-year time horizon with unstated Cycle length. Cost, mortality and QoL data for DMD, VAD and MM obtained from literature.	ot stated	Quality-adjusted survival: VAD: 1.42; MM: 0.26	**Base case** VAD: $355,059; MM: $123,290 **Sensitivity analysis** Not stated	**Base case** $200,540 / QALY vs. MM **Sensitivity analysis** $175,306-$371,558 / QALY vs. MM When VAD cost <$90,810 then ICER<$100,000/ QALY

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency, intervention, comparator)	ICER (per QALY gained)
		Discounting was not reported.				vs. MM
Magnetta 2018	2018	Markov-state transition model, with points of transition including survival and death.	Patients with DMD and advanced HF	**DT-VAD** 3.13 LYG on average Quality-adjusted survival was 1.99 QALYs **Medical management** 0.6 LYG on average Quality-adjusted survival was 0.26 QALYs	**Total costs for DT-VAD strategy** $435,602 **Total costs for medical management strategy** $125,696	The ICER for DT-VAD compared with medical management was $179,086/ QALY
Agboola 2010[141]	2020	**Model type** De novo 5-state partitioned survival model. **Health states** Early ambulatory Late ambulatory Early non-ambulatory Late non-ambulatory Death	Patients with DMD who began treatment at the age of 5 years	Costs are represented in $USD **Health sector perspective** **QALYs** Prednisone: 6.88 Deflazacort: 8.40 **LYs** Prednisone: 15.05 Deflazacort: 16.64 **Modified societal perspective** **QALYs** Prednisone: 6.88 Deflazacort: 8.40 **LYs** Prednisone: 15.05	Costs are represented in $USD **Health sector perspective** **Total Cost** Prednisone: 464,000 Deflazacort: 1,010,000 **Modified societal perspective** **Total Cost** Prednisone: 1,240,000 Deflazacort: 1,830,000	Results are represented in $USD **Health sector perspective** Cost per QALY Gained: 344,000 Cost per LY gained: 361,000 **Modified societal perspective** Cost per QALY gained: 371,000 Cost per LY gained: 390,000

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency, intervention, comparator)	ICER (per QALY gained)
				Deflazacort: 16.64		

Abbreviations: BSC – Best supportive care; DMD – Duchenne muscular dystrophy; DMDSAT – Duchenne muscular dystrophy Functional Ability Self-Assessment Tool; DT-VAD – Destination therapy ventricular assist device; EQ-5D-3L – Euro-QoL-5 Dimensions-3 Levels; 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; QoL – Quality of life; QALYs – Quality-adjusted life year; SA – Sensitivity analyses; UK – United Kingdom; US – United States; VAD – Ventricular assisted device; vs. – Versus.

B.3.2. Economic analysis

Santhera has sought to utilise the output of Project HERCULES, a unique initiative led by Duchenne UK to develop tools and evidence to support HTA and reimbursement decisions for new treatments for DMD. Project HERCULES brings together patient organisations, clinicians, academics, leading pharmaceutical companies, HTA agencies including NICE, and wider advisers, to build a robust evidence base for DMD. One of the key outputs from this initiative is the development of a cost-effectiveness model utilising the natural history model (NHM) as presented by Broomfield et al. at the 2020 European Conference on Rare Diseases & Orphan Products (ECRD).[91]

The Project HERCULES CEM was deemed the most relevant structure to model for this appraisal due to the wide network of stakeholders involved in the model development. Selection of a Markov model is aligned with the results of the SLR, which identified six studies, all of which used a Markov structure consistent with the Project HERCULES model. 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 and the anticipated licensed indication for vamorolone, the cost-effectiveness model considers a population of boys aged 4 years and above with DMD who are glucocorticoid-naïve. The average starting age has been set to 4.1 years in line with the average age of diagnosis in the UK.[92] This is similar to the average starting age in the VISION-DMD trial of 5.41 years.[6]

B.3.2.2. Model structure

The Project HERCULES CEM uses a cohort-based Markov model structure with disease-specific health states and was developed in Microsoft® Excel.

Project HERCULES model development

The Project HERCULES model structure was developed with multiple stakeholders' input from clinicians, academics, patients, and carers.[91] The process for defining model health states was as described below:

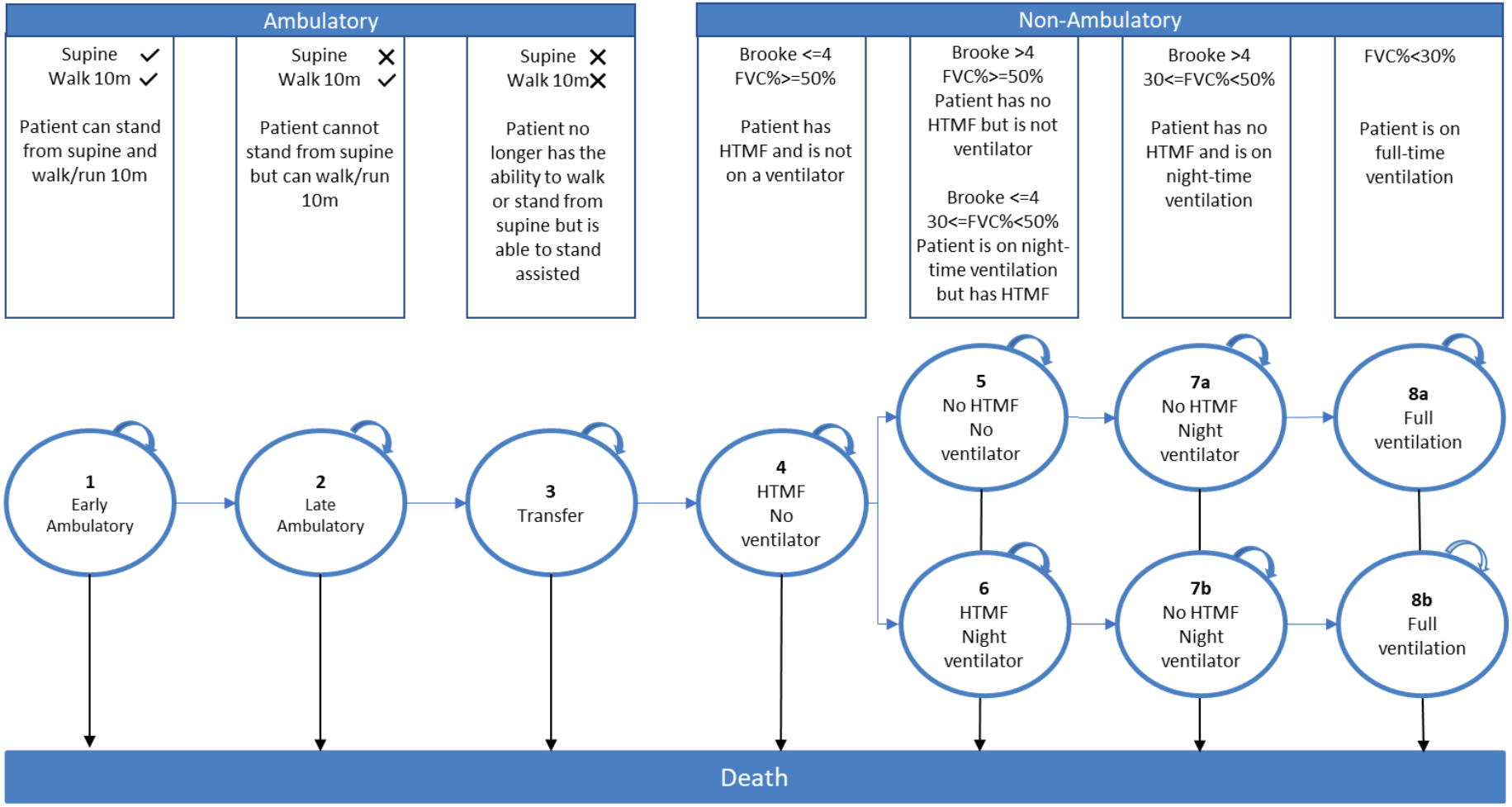
- A targeted literature review (TLR) of previous natural history studies and functional scales used in DMD was performed in MEDLINE through Project HERCULES.[93] This identified existing health state definitions, key milestones in disease progression, and outcomes captured in clinical trials.
- Following the review, a set of preliminary health states was defined. These were based on the conventional view of health states in DMD, such as those proposed by Bushby et al.[58]
- Health states were presented for stakeholder input, which included an advisory board meeting and follow-up questions with two neuromuscular specialists.
- Final health states were validated with a group of clinical experts, based on their extensive experience of treating patients with DMD, while bearing in mind limited data availability.

Health states were chosen using previously identified health states in published literature; input from clinicians, patients, and caregivers; and reflecting outcomes commonly collected in clinical trials and real-world practice. As such, the Project HERCULES model health states are considered well-validated and no changes to the structure were made for the vamorolone model.

Model health states

The model structure is illustrated in Figure 21.

Figure 21: Model schematic



Abbreviations: FVC - Forced vital capacity; HTMF – Hand-to-mouth function; m – Metres.

The model adopts a multi-state cohort structure, comprising ambulatory and non-ambulatory health states, plus an intermediate ‘Transfer’ health state, and death. A 1-month cycle length is used to align with the available clinical data in the VISION-DMD study and deemed granular enough to capture the impact of adverse events,[4] however, a scenario is included with a 3-month cycle length.

All patients passing through the Project HERCULES model progress through health states 1 to 3, which comprise the 'Early Ambulatory’, ‘Late ambulatory’ and ‘Transfer’ states. The ‘Ambulatory’ states are defined by three functional abilities:

- The ability to stand from supine,
- The ability to walk or run 10 metres,
- The ability to stand.

As displayed in Table 40, patients in the 'Early Ambulatory’ state are assumed to have all three abilities; with each health state transition, a functional ability is lost. In the ‘Late Ambulatory’ state, patients lose the ability to stand from supine and in the ‘Transfer’ state, patients can no longer walk or run 10 metres. In the ‘Transfer’ state, patients can stand for short periods and move a short distance, for example from a chair to the toilet. Based on the anticipated licence wording for vamorolone, all patients enter the model in health state 1; ‘Early ambulatory’.

Table 40: Definition of functional ability: ambulatory and transfer health states

Ambulatory status	**Ambulatory**		**Transfer**
Sub-states	**Early ambulatory**	**Late ambulatory**	**-**
Health states	**1**	**2**	**3**
Functional ability	Stand from supine Walk or run 10 metres Stand	Walk or run 10 metres Stand	Stand
Function lost	N/A	Stand from supine	Walk or run 10 metres

Abbreviation: N/A - Not applicable.

After the ‘Transfer’ state, all patients begin the ‘Non-Ambulatory’ stage with hand-to-mouth function (HTMF) and are able to breathe independently for 24 hours per day. At this point, the cohort of patients splits into one of two pathways, depending on which

of these functions is lost first. In health state 5, HTMF is lost first, however the patient retains the ability to breathe independently. In health state 6, HTMF is preserved, but night-time ventilation is required. Patients do not move between states 5 and 6.

In both health states 7a and 7b, patients have lost HTMF and require night-time ventilation only, in states 8a and 8b, all patients require full-time ventilation. The distinction between states a and b is the route by which the patient cohort reached these states. Transition probabilities in the NHM vary according to each pathway; however, the utilities and costs associated with 7a and 7b, and 8a and 8b are the same.

Non-ambulatory states are defined by a combination of the Brooke scale of upper extremity function (Brooke score) and the forced vital capacity (FVC) score. The Brooke score and FVC capture the key determinants of cost and HRQL 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. reported FVC%p (FVC percent predicted) by Brooke score and demonstrated that loss of upper extremity function correlated strongly with progressive loss of pulmonary function.[94]

In summary, the non-ambulatory health states are:

- Health state 4: the ability to self-feed, not on a ventilator (HTMF, no ventilator),
- Health state 5: unable to self-feed, not on a ventilator (No HTMF, no ventilator),
- Health state 6: the ability to self-feed, on night-time ventilation (HTMF, night-time ventilator),
- Health states 7a and 7b: unable to self-feed, on night-time ventilation (No HTMF, night-time ventilator),
- Health states 8a and 8b: full-time ventilation.

Table 41 summarises the definitions for health state membership in the Non-Ambulatory states according to the Brooke score and FVC score.

Table 41: Definition of functional ability by health state – non-ambulatory states

Ambulatory status	**Non-ambulatory**				
Sub-states	**HTMF, No Vent.**	**HTMF, Night Vent.**	**No HTMF, No Vent.**	**No HTMF, Night Vent.**	**Full Vent.**
Health states	**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; Vent. - Ventilation.

Key model features

The NICE reference case states that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any difference in costs or outcomes between the medicines being compared.[95] Patients in the VISION-DMD study had an average age of 5.41 years at baseline[6], and data from Vry et al.[92] indicate that the average age at diagnosis in UK practice is 4.1. Therefore, a 50-year time horizon is used to align with the expectation that patients generally do not live beyond 45 years[53], while acknowledging data on long-term mortality are sparse and some patients may live for longer. The impact of alternative time horizons is explored in scenario analyses.

Over the time horizon, each cohort accrues the costs and outcomes faced when patients transition between the health states based on-treatment-specific transition matrices or leave the model by transitioning to the death state. A half-cycle correction is applied in the adapted model, as per the NICE reference case.[95]

For each cycle, total costs and quality-adjusted life years (QALYs) are calculated based on the distribution of patients across the health states and death. These are accumulated over the model time horizon for the two cohorts from which incremental results and the cost per QALY are determined. Costs and outcomes are discounted at 3.5% per annum in line with the NICE reference case.[95] An alternative discount rate of 1.5% is explored in scenario analyses.

The model adopts a UK NHS and PSS perspective on costs and in line with the NICE reference case.[95] The perspective on outcomes considers all direct health effects, whether for patients or, when relevant, carers, in line with the NICE reference case. As such, the base case considers the quality of life impact to carers as well as patients living with DMD.

Societal costs are key components in evaluating the cost-effectiveness of treatments in DMD given the substantial burden faced by patients and carers alike, as discussed in Section B.1.3. Health condition and position of the technology in the treatment pathway Once ambulation is lost and respiratory decline begins, carer burden and time off work increases, emphasising the wider importance of slowing disease progression.[56] Caring for DMD patients is time-consuming and has a severe negative impact in several aspects of daily living including patients and parents' productivity. The care of patients becomes 24/7 once patients are on full-time assisted ventilation. Without informal care, this level of care would otherwise be provided by paid professionals, the cost of which would be absorbed by the NHS and PSS. In the context of HTA, these findings emphasise the importance of considering all costs, not only those attributed to formal care, in the evaluation of treatments for chronic diseases such as DMD to allow for a meaningful appraisal of treatment benefits to patients and carers alike. It is therefore noted that the NHS & PSS perspective adopted for this appraisal in line with the NICE reference case may miss key aspects of the disease which affects patients and their carers' lives.

Table 42 summarises the features of the economic analysis for this appraisal with respect to the NICE reference case.

Table 42: Features of the economic analysis

	Current evaluation	
Factor	**Chosen values**	**Justification**
Time horizon	50 years (Lifetime)	DMD is a life-long condition that reduces life expectancy significantly, with a median life expectancy of 29.9 years (range 21.0-36.2) with ventilatory support.[20] As such a 50-year time horizon is sufficient to capture all important differences in costs or outcomes between the treatments. This is in line with the NICE reference case.
Cycle length	1 month	A 1-month cycle length is considered appropriate to accurately capture all differences in efficacy, health transitions (notably allowing the inclusion of the transfer state) and adverse events.
Perspective	UK NHS/PSS	This perspective is in line with the requirements of the NICE reference case.
Discount	3.5%	Discounting is line with the requirements of the NICE reference case.
Source of utilities	Published literature	Disutilities associated with adverse events and specific comorbidities are taken from relevant published literature.
Source of health state utilities	BOI study (Evans et al. 2020)	The BOI study[96], steered by Project HERCULES is a descriptive, retrospective, cross-sectional multi-site prevalence based study informed by physicians, patients and carers based in the UK and is therefore suitable for a UK HTA submission. EQ-5D data is collected in the vision-DMD trial but lacked sensitivity due to the nuances of DMD.[51] The utilities from the BOI study are from the DMD-QoL scale and based on the health states rather than age. These utilities values are well suited to the model structure and seen as the most appropriate reflection of QoL for those with DMD. Carer utilities were also taken from the BOI study.
Source of costs	NHS reference costs, BNF drugs costs and published literature	Resource utilisation costs associated with AEs are taken the NHS references costs as these are the best reflection of UK costs in practise. Treatment costs are taken from the BNF as they are the costs used by the NHS for treatments. Remaining costs are taken from UK published literature.
Source of health state costs	BOI study (Evans et al. 2020)	Carer and indirect costs are taken from the BOI study. The BOI study steered by Project HERCULES is a descriptive, retrospective, cross-sectional multi-site prevalence based study informed by physicians, patients and carers based in the UK and is therefore suitable for a UK HTA submission. The study is seen as to most accurately capture the resource utilisation and burden associated with DMD patients and carers. The costs are also designed around the structure of the model. Carer and indirect costs associated with the health states are also taken from this study.

Abbreviations: AE – Acute events; BNF – British National Formulary; BOI – Burden of Illness; DMD – Duchenne muscular dystrophy; EQ-5D, EuroQol Five Dimension; PSS – Personal Social Service; NICE – National Institute for Health and Care Excellence; NHS – National Health Service; UK – United Kingdom; QoL – Quality of Life.

Intervention technology and comparators

The intervention in the model is vamorolone with a starting dose of 6 mg/kg/day for patients aged four and overin line with the SmPC.[11] Patients may down titrate to 4 mg/kg/day or 2 mg/kg/day due to tolerability as required. As the starting age in the model is 4.1 years, in the base case all patients within the model begin on 6 mg/kg/day. In line with the final scope shown in Table 1, established clinical management, described from here on as standard of care (SoC) is the primary comparator in the model. SoC comprises prednisone and deflazacort, with details of the dosing used in the model for all comparators obtained from DMD Care Considerations Working Group guidelines and shown in Table 43. The down-dosing strategies applied for SoC in the model reflect DMD treatment guidelines, however it is acknowledged that in practice other strategies may be used, including intermittent dosing as seen in VISION-DMD and FOR-DMD. As described in Section B.1.3. Health condition and position of the technology in the treatment pathway, glucocorticoids are associated with substantial AEs and as such, in clinical practice, many patients receive suboptimal doses to help manage these effects or discontinue from treatment entirely. The model follows patients from the point of starting treatment; therefore all patients start on optimal dosing for both treatment arms but may dose-reduce or discontinue as the model continues; these transitions are described in further detail in Section 02.

Table 43: Dosing regimens in the economic model

Drug	Starting dosing regimen	Dose reduction regimen	Source
Intervention			
Vamorolone	• Aged 4 years and older: 6.0 mg/kg/day administered orally	May be down-titrated to either below based on individual tolerability: • 4.0 mg/kg/day administered orally • 2.0 mg/kg/day administered orally	SmPC[11]; VISION-DMD[4]
SoC			
Prednisone	0.75 mg/kg/day administered orally	0.53 mg/kg/day administered orally	25-33% dose reduction based on Birnkrant et al.[16]
Deflazacort	0.9 mg/kg/day administered orally	0.64 mg/kg/day administered orally	

Abbreviations: Mg – Milligram; Kg – Kilogram; SoC – Standard of care.

B.3.3. Clinical parameters and variables

As described in Section B.2.2. List of relevant clinical effectiveness evidence, the VISION-DMD trial is the pivotal study underpinning the anticipated licensed indication. Additionally, two further studies were conducted including FOR-DMD and the LTE study, exploring longer-term data for SoC and vamorolone respectively; both are described in Section B.2.2. List of relevant clinical effectiveness evidence. As such, clinical effectiveness data from VISION-DMD, FOR-DMD and the LTE were used to inform the economic model, alongside the NHM transitions within the Project HERCULES CEM. Together, these data sources help form a complete and holistic representation of DMD patients as they transition through differing stages of DMD.

B.3.3.1. Baseline demographics

As described in Section B.3.3.2, the average age at diagnosis in the UK is 4.1 years old.[92] As a scenario, the average baseline age of randomised patients forming the ITT population of the VISION-DMD study (5.41 years; Section B.2.3.2) was tested. All patients were assumed to enter the model in the early ambulatory health state, based on the assumption that in UK clinical practice patients would be in this state at diagnosis.[4]

B.3.3.2. Derivation of transition probabilities

Data from the VISION-DMD trial were assessed to evaluate whether transition probabilities could be obtained from the pivotal trial. Due to the short follow-up of 24-weeks, a limited number of patients had transitioned out of the 'early ambulatory' health state, with patients on either treatment arm having only transitioned to the second health state of the model at the furthest. Due to these limitations, very minimal transition probabilities were available. As the creation of substantial transition probabilities from VISION-DMD were not feasible, transitions from the NHM have been used in the model.

Natural history model

As detailed in Section B.2.12., vamorolone 6.0 mg/kg/day showed comparable efficacy to prednisone 0.75 mg/kg/day in VISION-DMD. The NHM is therefore used to populate transition probabilities for vamorolone and SoC while patients remain on the starting

dosing regimen. This was deemed a conservative approach as reduced dose glucocorticoids are expected to be less efficacious when compared to optimal dose glucocorticoids and vamorolone; the NHM may therefore underestimate the efficacy of vamorolone and optimal dose glucocorticoids.

The NHM was created to provide new insights into the trajectory of disease and to inform economic evaluations of new therapies. The primary data source informing the 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 used comprised anonymised individual patient data (IPD) from 11 international data sources, including NH studies, placebo arms of clinical trials and registry data. The patient cohort used to generate the NHM had 80% of patients being on steroids. However, there was no mention of the dosing scheme therefore this is an uncertainty associated with use of the NHM. Clinical validation indicated that the NHM would be broadly reflective of SoC in the UK, while noting that without knowing dosing regimens received in the NHM it is not possible to know for certain.

The NHM assumed a constant progression rate in each state, and that the mortality rate varies only by health state. Previous models have considered age-based hazards; however, these models have generally considered broader health state definitions and fit survival models to Kaplan-Meier (KM) data using age as a time scale. This means that estimated progression rates are not conditional on having reached the previous state. Mortality data were extracted from published KM curves exploring life expectancy in DMD.[53] An increased rate of mortality was implemented after age 30 years in state 8A/8B. Age 30 was selected as a mid-point in the follow-up, approximately corresponding to the median survival of patients in the mortality dataset and in the published literature.

The NHM assumed that DMD is progressive, with no backwards transitions permitted and that patients may only progress to adjacent states. Both assumptions were validated through clinician interview and confirmed as appropriate.

No data were available on the transitions to and from the Transfer state; instead, this was informed by data from an elicitation exercise. The NHM fit was iterated until convergence of all transition rates.

Table 44 and Table 45 present the transition intensities produced by the NHM, split by patients under and over the age of 30, respectively.

Table 44*:* Transition probabilities from the NHM below 30

	State 1	State 2	State 3	State 4	State 5	State 7A	State 8A	State 6	State 7B	State 8B	State 9
State 1	98.64%	1.36%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
State 2	0.00%	97.61%	2.38%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%
State 3	0.00%	0.00%	94.72%	5.27%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%
State 4	0.00%	0.00%	0.00%	95.30%	2.37%	0.00%	0.00%	2.28%	0.00%	0.00%	0.05%
State 5	0.00%	0.00%	0.00%	0.00%	98.25%	1.64%	0.00%	0.00%	0.00%	0.00%	0.11%
State 7a	0.00%	0.00%	0.00%	0.00%	0.00%	96.45%	3.29%	0.00%	0.00%	0.00%	0.25%
State 8a	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.67%	0.00%	0.00%	0.00%	0.33%
State 6	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	98.24%	1.51%	0.00%	0.24%
State 7b	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	95.59%	4.11%	0.30%
State 8b	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.68%	0.32%
State 9	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%

Abbreviations: NHM - Natural history model.

Table 45: Transition probabilities from the NHM above 30

	State 1	State 2	State 3	State 4	State 5	State 7A	State 8A	State 6	State 7B	State 8B	State 9
State 1	98.64%	1.36%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
State 2	0.00%	97.61%	2.38%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%
State 3	0.00%	0.00%	94.72%	5.27%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%
State 4	0.00%	0.00%	0.00%	95.30%	2.37%	0.00%	0.00%	2.28%	0.00%	0.00%	0.05%
State 5	0.00%	0.00%	0.00%	0.00%	98.25%	1.64%	0.00%	0.00%	0.00%	0.00%	0.11%
State 7a	0.00%	0.00%	0.00%	0.00%	0.00%	96.45%	3.29%	0.00%	0.00%	0.00%	0.25%
State 8a	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.35%	0.00%	0.00%	0.00%	0.65%
State 6	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	98.24%	1.51%	0.00%	0.24%
State 7b	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	95.59%	4.11%	0.30%
State 8b	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.35%	0.65%
State 9	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%

Abbreviations: NHM - Natural history model.

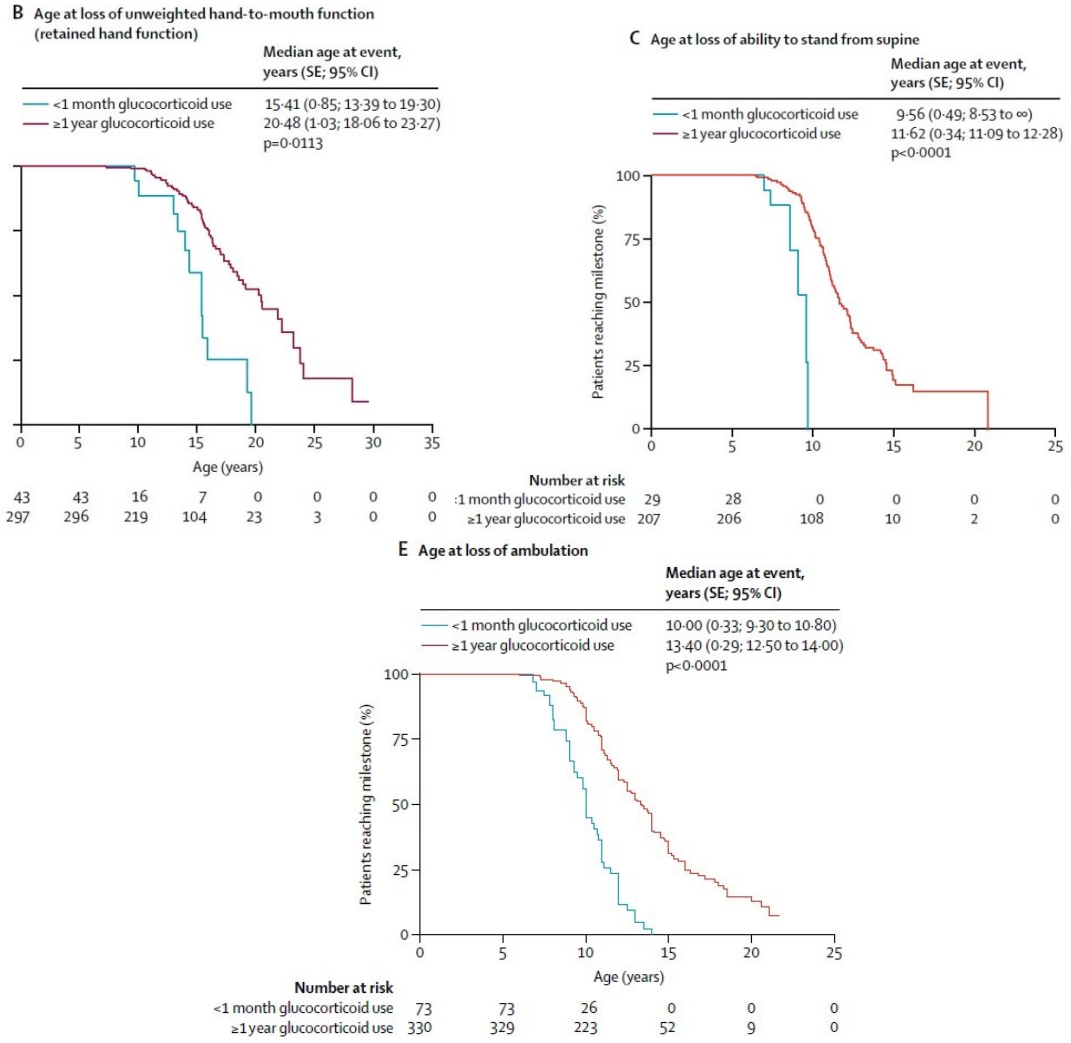
As an additional check for clinical plausibility, the per cycle rate of death was compared to the mortality rate in the general population matched for gender and age in each cycle, using National life tables for England and Wales from the ONS.[97] If the matched general population rate was higher, this was used in the model for that cycle.

Comparative efficacy of treatments

McDonald et al.[64] reported KM analyses of time to ambulatory milestones in DMD patients, split by patients who were on-treatment with glucocorticoids for over 1 year, and those who were on glucocorticoid treatment for <1 month or were never treated. The paper used data from the CINRG registry recorded between 2006 and 2016. It was assumed that the ≥1 year cohort reflects on-treatment with vamorolone or optimal dose corticosteroids, while the <1 month cohort reflects efficacy for patients who have discontinued (i.e., those receiving no treatment). This assumption was tested in clinical validation; the clinician noted McDonald et al. is not ideal as the corticosteroid arm was very broadly defined, potentially leading to a lot of variation in what corticosteroid regimens are included. Despite the drawbacks, the clinician noted that this is an appropriate source and assumption to make.

Milestones that aligned to model health states (age at loss of hand-to-mouth function, age at loss of ability to stand from supine, and age at loss of ambulation) were digitized and cox-proportional hazard analysis conducted to generate a hazard ratio (HR) for the ≥1 year and <1 month steroid use arms. KM curves are presented in Figure 22 B, C and E for age at loss of hand-to-mouth function, age at loss of ability to stand from supine, and age at loss of ambulation, respectively.

Figure 22: Kaplan-Meier data for ambulatory milestones from McDonald et al[64]



Abbreviations: CI - Confidence interval; SE - Standard error. Key: B: Age at loss of hand-to-mouth function; C: Age at loss of ability to stand from supine; E: Age at loss of ambulation.

The resulting HRs for each milestone are presented in Table 46, along with the assumptions made to extend to further health states.

Table 46: Hazard ratios from McDonald et al. and approach for remaining health states

Health state transitions	HR (CI)	Source
To state 2 - Late ambulatory	2.41 (0.29, 8.31)	McDonald et al.[64]
To state 3 - Transfer	1.41 (0.18, 7.66)	Assumed same as to HS 4
To state 4 - HTMF, no ventilation	1.41 (0.18, 7.66)	McDonald et al.[64]
To state 5 - No HTMF, no ventilation	1.16 (0.35, 3.31)	McDonald et al.[64]
To state 7a - No HTMF, night-time ventilation	1.16 (0.35, 3.31)	Assumed same as to HS 5
To state 8a - Full-time ventilation	1.16 (0.35, 3.31)	
To state 6 - HTMF, night-time ventilation	1.16 (0.35, 3.31)	

Health state transitions	HR (CI)	Source
To state 7b - No HTMF, night-time ventilation	1.16 (0.35, 3.31)	
To state 8b - Full-time ventilation	1.16 (0.35, 3.31)	

Abbreviations: CI - Confidence interval; HR - Hazard ratio; HS - Health state.

To estimate the efficacy of optimal versus suboptimal steroid use, data from FOR-DMD were sought. The relative efficacy of the daily prednisone and intermittent prednisone arms from FOR-DMD were compared, as shown in

Table 47

	Event frequency (%)		Hazard ratio 98.3% CI P-value
	Daily prednisone	**Intermittent prednisone**	
Time to loss of the ability to walk	3 (5)	9 (14)	0.44 (0.09, 2.20) p = 0.22
Time to loss of the ability to rise from the floor	7 (11)	17 (26)	0.36 (0.12, 1.09) p = 0.03

. The event frequency and HR of loss of ability to rise from the floor (equivalent to health state 2 ‘Late ambulatory’) and loss of ability to walk (equivalent to health state 3 ‘Transfer’) have been taken from Guglieri et al.[76] The resulting HRs estimate worse efficacy for intermittent prednisone than with no treatment when naively compared to the HRs from McDonald et al.[64] (Table 46), thereby giving implausible results. To help address this, clinician validation was sought to understand how steroid efficacy compares by dosing regimen in practice. The clinical expert considered suboptimal steroids to have nearer 60% of the efficacy of optimal full dosed steroids compared to the efficacy of no treatment. Due to paucity of data, McDonald et al. is the only source available for estimating the relative efficacy of SoC and no treatment. Therefore, as a mid-way estimate between the FOR-DMD data and the clinical validation figure, an estimate of 40% efficacy was used in the base case. This is applied by weighting the transition probabilities of SoC and no treatment for each transition in the Markov Trace for SoC. It is acknowledged that this is a source of uncertainty in the model; to test the uncertainty around this input, scenarios of 60% (reflecting clinical opinion) and 20% (reflecting a closer estimate to FOR-DMD) are tested.

Table 47: Time to loss of ambulatory milestones in FOR-DMD (Guglieri et al.)[76]

	Event frequency (%)		Hazard ratio 98.3% CI P-value
	Daily prednisone	**Intermittent prednisone**	
Time to loss of the ability to walk	3 (5)	9 (14)	0.44 (0.09, 2.20) p = 0.22
Time to loss of the ability to rise from the floor	7 (11)	17 (26)	0.36 (0.12, 1.09) p = 0.03

Abbreviations: CI - Confidence interval.
Source: Guglieri et al.[76]

B.3.3.3. Adverse events

The impact of adverse reactions as reported in VISION-DMD[4] were explored to evaluate the consequences on health-related quality of life for patients experiencing the event. Glucocorticoids have been shown to induce severe side effects in patients with DMD, resulting in compliance issues and patients receiving down-titrated doses to mitigate them. These side effects are particularly pertinent in patients with DMD, as this patient population receives treatment with glucocorticoids during childhood and adolescence, where key physical and emotional development occurs. It has been shown that patients gain more benefit from steroidal treatment if they are not on down-titrated dosing. As vamorolone offers the same treatment efficacy (Section B.2.6) with an improved safety profile, patients are able to gain the full benefit of steroidal treatment with reduced adverse effects and higher compliance. Due to this, the inclusion of the effects of treatment and compliance rates have been incorporated into the model. Adverse reactions have been categorised into AESI and acute events.

An AESI is defined as an adverse event of scientific and medical concern specific to steroidal users and are displayed in B.2.10.1.5. These vary in incidence by treatment arm, using VISION-DMD data; placebo rates from VISION-DMD are used within the model to represent rates for patients who have discontinued from active treatment. Only moderate or severe AESIs from VISION-DMD were included in the CEM due to these having the greatest impact on patient quality of life, treatment discontinuation and associated health service costs. The 24-week rate of moderate and severe AESIs in VISION-DMD is presented in Table 48.

Acute events, displayed in B.2.10.1.5. Adverse events of special , are defined as events which are severe and sudden in onset. Acute event rates by treatment arm were taken from VISION-DMD with placebo rates used for patients who have discontinued from treatment as above. The 24-week rate of acute events in VISION-DMD is presented in Table 49.

For patients who down titrate due to adverse events, a lower rate of adverse events was calculated based on a rate ratio of daily prednisone to intermittent prednisone adverse events in FOR-DMD and applying it to the rate of adverse events used in the corticosteroid arm from VISION-DMD; rates and rate ratios are presented in Table 50. The resulting rates for moderate to severe AESIs and acute events used for each modelled arm in the CEM are presented in Table 51. Data on stunted growth were not available from VISION-DMD or FOR-DMD and were taken from published literature reporting the proportion of boys with DMD on steroids who have short stature over 6 years.[98]

Table 48: Moderate to severe AESI rates by treatment in VISION-DMD

Treatment	Vamorolone	Prednisone	Placebo	Source
Weight gain	0.00%	3.23%	0.00%	VISION-DMD Santhera data on file; rate over 24 weeks.
Behavioural issues	0.00%	25.81%	3.45%	
Cushingoid effects	3.57%	0.00%	0.00%	
Immune suppressed/infection	0.00%	12.90%	10.34%	
GI symptoms	0.00%	3.23%	3.45%	
Diabetes	0.00%	0.00%	0.00%	
Skin/Hair change	0.00%	3.23%	0.00%	

Abbreviations: AESI – Adverse event of special interest; GI – Gastrointestinal.

Table 49: Acute events rates by treatment

Treatment	Vamorolone	Prednisone	Placebo	Source
Diarrhoea	7.1%	6.5%	3.4%	VISION-DMD CSR[6]; rate over 24 weeks
Vomiting	14.3%	6.5%	6.9%	
Pyrexia	0.0%	6.5%	20.7%	
Cough	7.1%	9.7%	3.4%	

Table 50: FOR-DMD AESI and acute event rates by prednisone arm[99]

AESI	0.75mg/kg daily	10mg intermittent	Rate ratio
Weight gain	0.12	0.08	0.64
Behavioural issues	-	-	0.82*
Cushingoid effects	0.1	0.10	0.96
Immune supressed/infection	0.2	0.13	0.67

GI symptoms	-	-	0.82*
Diabetes	-	-	0.82*
Skin/Hair change	-	-	0.82*
Stunted Growth	-	-	0.82*
Acute events			
Diarrhoea	0.2	0.15	0.77
Vomiting	0.34	0.29	0.85
Pyrexia	0.2	0.19	0.96
Cough	0.26	0.23	0.89

Abbreviations: AESI – Adverse event of special interest; GI – Gastrointestinal.
* Indicates events for which no data were available; in this case, the average rate ratio was used.

Table 51: Adverse event 1-month cycle rates by treatment used for modelling

Treatment	Vamorolone	SoC (optimal dose)	SoC (sub-therapeutic dose)	Placebo	Source
Diarrhoea	1.33%	1.20%	0.92%	0.63%	VISION-DMD; rate over 24 weeks Sub-therapeutic SoC AE rates calculated from ratio in FOR-DMD.
Vomiting	2.75%	1.20%	1.02%	1.29%	
Pyrexia	0.00%	1.20%	1.15%	4.11%	
Cough	1.33%	1.83%	1.62%	0.63%	
Weight gain	0.00%	0.59%	0.38%	0.00%	
Behavioural issues	0.00%	5.26%	4.32%	0.63%	
Cushingoid effects	0.66%	0.00%	0.00%	0.00%	
Immune suppressed/infection	0.00%	2.47%	1.66%	1.96%	
GI symptoms	0.00%	0.59%	0.48%	0.63%	
Diabetes	0.00%	0.00%	0.00%	0.00%	
Skin/Hair change	0.00%	0.59%	0.48%	0.00%	
Stunted growth	0.00%	1.75%	1.44%	0.00%	Wong et al.; rate over 6 years

Abbreviations: GI – Gastrointestinal; SoC – Standard of care.

To explore uncertainty around AESIs, a scenario is included in which AESIs of all grades are included in the model. This scenario uses the rates provided in Table 36 (Section B.2.10.1.5).

B.3.3.4. Bone health

Fractures

As mentioned in Section B.1.3. Health condition and position of the technology in the treatment pathway, boys with DMD are at an increased risk of fractures that increases throughout their lives[35,36], with the impact of progressive myopathy being further exacerbated by the ototoxicity of glucocorticoids.[29] It is widely accepted across the literature that these fractures can often compound, leading to more severe and regular fractures as patients grow older.[100] Vertebral fractures can often be asymptomatic so go undetected without regular testing, these fractures, even if asymptomatic, are

predictive of future fractures. Fractures in the model are therefore captured as a rate per health state to allow the functionality for an increasing rate of fractures as the disease progresses.

The rates and time frame for each rate is applied to are shown in Table 52 and Table 53 for spinal vertebral and other fractures (long bone), respectively. The rates of fractures are based on data from Perera et al. 2016. The authors presented KM curves for the probability of vertebral and long bone fractures for ages 0-18 for chronic corticosteroid use and non-chronic corticosteroid use.[35] All fractures recorded were symptomatic and presented with pain. Asymptomatic fractures are often left untreated in clinical practice as without the presentation of pain and due to a lack of regular testing, fractures are often left untreated. Due to this, the treatment of moderate to severe asymptomatic vertebral fractures is recommended[16] and suggests that the rates presented actually underestimate the true burden of fractures seen in DMD patients. The probabilities for the chronic corticosteroid use, based on an average daily prednisone dose of 0.53mg/kg, were converted into incidences by age, which were then categorised into rates for health states based on the average ages for each health states for the corticosteroid (SoC) arm using the NHM model. The age-related probabilities were converted into rates per health state according to how long on average patients spend in each health state. These rates were then converted into one-month probabilities in the model.

To calculate the rate of fractures by health state in the vamorolone arm, vertebral fracture data from the LTE study[69] and FOR-DMD over 36 months were used to calculate a rate ratio of 0.430 compared to SoC corticosteroid use.[69] For the SoC arm a weighted average of vertebral fracture for prednisone and deflazacort was used. The rates of fractures for vamorolone by health state were calculated by applying this ratio to the SoC rate of fractures.

The resulting rates used in the model are shown in Table 52 and Table 53, respectively for spinal and other fractures.

Table 52: Spinal vertebral fracture rate by health state

Health state	Vamorolone	SoC	No treatment	Time frame (weeks)
1 - Early ambulatory	0.00%	0.0%	0.0%	104
2 - Late ambulatory	0.00%	0.0%	0.0%	208
3 - Transfer	0.08%	0.13%	0.0%	104
4 - HTMF, no ventilation	0.82%	2.00%	0.0%	52
5 - No HTMF, no ventilation	0.47%	0.83%	0.0%	260
6 - HTMF, night-time ventilation	0.47%	0.83%	0.0%	260
7b - No HTMF, night-time ventilation	0.47%	0.83%	0.0%	260
8b - Full-time ventilation	0.47%	0.83%	0.0%	260

Abbreviations: HTMF – Hand-to-mouth function; SoC – Standard of care.

Table 53: Other fracture rate by health state

Health state	Vamorolone	SoC	No treatment	Time frame (weeks)
1 - Early ambulatory	0.00%	0.13%	0.29%	104
2 - Late ambulatory	0.00%	0.20%	0.00%	208
3 - Transfer	0.13%	0.00%	0.60%	104
4 - HTMF, no ventilation	2.00%	0.79%	0.58%	52
5 - No HTMF, no ventilation	0.83%	0.22%	0.52%	260
6 - HTMF, night-time ventilation	0.83%	0.22%	0.52%	260
7b - No HTMF, night-time ventilation	0.83%	0.22%	0.52%	260
8b - Full-time ventilation	0.83%	0.22%	0.52%	260

Abbreviations: HTMF – Hand-to-mouth function; SoC – Standard of care.

Scoliosis

The model also captures scoliosis, an important factor in DMD as described in Section B.1.3. Health condition and position of the technology in the treatment pathway. Scoliosis is captured indirectly by the proportion of individuals requiring spinal fusion surgery with a disutility arising from surgery itself. Patients are eligible for spinal surgery in the model from 15-25 years in line with patients in the model starting to lose ambulation from age 15 onwards based on data from McDonald et al.[64] Within the model, it is assumed patients have surgery 4 years following loss of ambulation based on McDonald et al. in which both chronic and non-chronic corticosteroid users had spinal surgery on average 4-5 years after loss of ambulation.[64] The specific HRQL impact of scoliosis is assumed to be captured within the health states utilities.

McDonald et al. 2018 presented data on the rate of spinal fusion surgery for steroid patients.[64] The study reviewed the impact of long-term steroid use on the quality of life of those with DMD and found that 72 of 248 (29%) non ambulatory patients had spinal fusion surgery over 10 years. The study was largely made up of individuals who had

been treated with corticosteroids (only 13% had never been treated with corticosteroids). However, clinical validation indicated that in reality, nearer 10% of patients on-treatment with steroids have spinal fusion surgery in clinical practice, while for patients receiving no treatment this rate is nearer 90%. In lieu of other data, rates provided by the clinician were used in the model base case and can be found below in Table 54. The risk of spinal surgery is assumed to remain constant across a treatment arm with patients not switching to a different rate when they discontinue or lower their dosing. There are several causes that lead to the need to spinal surgery that cannot all be reversed upon switching/changing their treatment, such as past fractures, so their long-term treatment pathway has been assumed to define their risk of spinal surgery over their lifetime. It was assumed that the rate of spinal fusion surgery for vamorolone was equivalent to the rate for SoC.

Table 54: Rates of spinal surgery

Scoliosis	Vamorolone	SoC	No treatment
Proportion of patients that receive spinal surgery over 10 years	10%	10%	90%
Time till surgery after loss of ambulation (years)	4	4	4

Abbreviations: SoC – Standard of care.

B.3.3.5. Discontinuation

Discontinuation for vamorolone and SoC were taken from VISION-DMD and CINRG, respectively. Within VISION-DMD, 28/30 (93.3%) of patients completed the study through to week 24, while [redacted] completed the study through to week 48.[4,5] Decision Support Unit (DSU) Technical Support Document (TSD) 14 states to attempt survival analysis using six standard parametric curves: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma. This was attempted, however, given the small patient numbers, the parametric curves produced implausible results. Exponential curves were therefore fitted to the above data points and are used in the model base case, given this is the simplest parametric model.

Additionally, a stopping rule for vamorolone is applied within the model. The base case assumes that patients will stop treatment with vamorolone upon reaching night-time ventilation (state 6). The rationale for this stopping rule is that glucocorticoid treatment

is primarily used to slow down the progression of muscle weakness and preserve function[57]; once a patient has lost the ability to breathe without ventilator support, the perceived benefits of steroids in preserving skeletal muscles are no longer applicable. In addition, the efficacy of vamorolone has not been demonstrated in patients requiring night-time ventilation, therefore it is unclear whether potential benefits will outweigh the potential risks beyond this milestone. Alternative stopping rules have been explored within the scenario analyses.

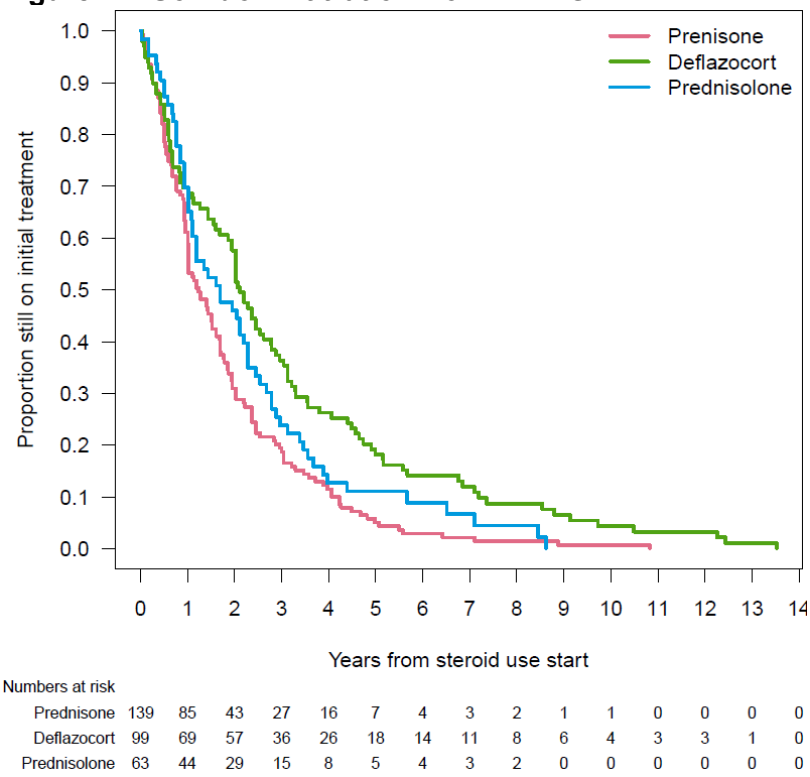
Discontinuation data from CINRG are shown in Figure 23. The prednisone and deflazacort arm data were used within the CEM and weighted 84% prednisone and 16% deflazacort according to the BOI study (Evans et al 2020).[96] Due to time constraints, it was not possible to conduct parametric modelling for these data; therefore as a simplifying assumption an exponential distribution is used for both arms.

It is assumed that patients who discontinue from treatment with vamorolone or SoC receive no treatment, and therefore the efficacy and safety data of the 'no treatment' arm are applied to these patients.

Figure 23: SoC discontinuation from CINRG

Down-titration for SoC was also calculated from the CINRG data, with the proportion of patients still on their initial treatment dosage taken over 15 years. The down-titration data are presented in Figure 24. The same approach of weighting prednisone and deflazacort arms as described above was implemented. As both KM curves are complete, there was no need to extrapolate the data.

Figure 24: SoC down-titration from CINRG



Down-titration for vamorolone from 6.0 mg/kg to 4.0 mg/kg was not part of the VISION-DMD protocol, so a reduction from 6.0 mg/kg to 4.0 mg/kg has been applied over time within the model at a constant rate because data from the named patient programme (NPP) indicated that the average dose received in UK clinical practice is 4.55 mg/kg/day, therefore the model base case reflects this via a transition to this average dose between months three and six of the model. Scenarios are tested in which all patients down titrate to 4.0 mg/kg/day based on clinical validation, and in which 50% of patients down titrate, expected to reflect the upper limit of average dosing in practice. It is acknowledged by the company that the average down-titrated dose in clinical practice and the timing of down-titration is a data limitation of the model.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality of life data from clinical trials

EQ-5D data were not available from the VISION-DMD trial.[4] Subsequently, the values selected for the model base case were taken from the literature and described later in this section. The EQ-5D scale has been noted to be lacking in sensitivity due to the

nuances of DMD, as demonstrated in Powell et al.[51] and as previously discussed in Section B.1.3. Health condition and position of the technology in the treatment pathway.

B.3.4.2. Mapping

No mapping was undertaken due to the limitations reported for the EQ-5D data.

B.3.4.3. Health-related quality of life studies

The SLR introduced in Section B.3.1 also aimed to identify relevant HRQL studies from the published literature. Full details of the SLR search strategy, study selection process and results are presented in Appendix H. Overall, 22 studies were identified; these are presented in Appendix H. The Landfeldt et al. 2017 study was the key study used within the economic analysis due to its similarities to the health states within the model, use of patient-measured utilities and use in previous DMD submissions (Table 55).[89] The remaining studies were deemed inappropriate due to using carers as a proxy, less synthesis with the model's health state or not utilising a UK based cohort.

Table 55: Summary of Landfeldt et al., 2017[89]

Study	**Landfeldt et al., 2017**
Population in which health effects were measured	Children with DMD aged 5 years upon commencement of the study, and their caregivers.
Information on recruitment	Cross-sectional, observational study of patients with DMD from Germany, Italy, the UK, and the USA identified through national DMD registries that form part of the global TREAT- NMD Neuromuscular Network.
Interventions and comparators	Hypothetical treatment and SoC - ambulatory status in model II.
Sample size	Not reported in model I and II.
Response rates	Not reported
Description of health states	Model I: DMDSAT score 0 through 23 in patients and caregivers. Model II: early ambulatory; late ambulatory; early non- ambulatory; and late non- ambulatory in patients and caregivers. Model III: no ventilation; night-time ventilation; and day- and night- time ventilation in patients and caregivers.
Adverse reactions	N/A
Appropriateness of health states given the condition and treatment pathway	Appropriate
Method of elicitation	Patients' utilities were measured by primary caregivers completing the HUI questionnaire on their behalf. Caregivers completed the EQ-5D-3L

	questionnaire.
Method of valuation	Patient utilities were derived using HUI Mark 3 multi-attribute health status classification system. Caregiver utilities were derived using UK EQ-5D index evaluation.
Mapping	Mapped to specified model states in a previous publication fitting generalised linear regression models assuming a gamma distribution with a log link.
Uncertainty around values	N/A
Consistency with reference case	HUI is not consistent with the reference case. EQ-5D is consistent with the preferred measure of health-related quality of life in the reference case.
Results with confidence intervals	**Data used in model I** DMDSAT score of 23: • Patient (SE): 0.879 (0.037) • Caregiver (SE): 0.862 (0.016) Multiplier per reduction in DMDSAT by 1 point: • Patient (SE) 0.905 (1.003) • Caregiver (SE): 0.995 (1.001) **Data used in model II** Early ambulatory: • Patient (SE): 0.699 (0.036) • Caregiver (SE): 0.858 (0.017) Late ambulatory: • Patient (SE): 0.607 (0.029) • Caregiver (SE): 0.839 (0.017) Early non- ambulatory: • Patient (SE): 0.224 (0.014) • Caregiver (SE): 0.784 (0.021) Late non- ambulatory: • Patient (SE): 0.146 (0.010) • Caregiver (SE): 0.810 (0.018) **Data used in model III** No ventilation: • Patient (SE): 0.518 (0.027) • Caregiver (SE): 0.837 (0.014) Night-time ventilation: • Patient (SE): 0.146 (0.010) • Caregiver (SE): 0.775 (0.030) Day- and night- time ventilation:

	• Patient (SE): 0.051 (0.010) • Caregiver (SE): 0.774 (0.033)
Appropriateness of the study for cost-effectiveness analysis	Different measurement method for patients and caregivers; inappropriate. Tested as a scenario.

Abbreviations: DMD - Duchenne muscular dystrophy; DMDSAT - Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool; EQ-5D - EuroQol Five Dimension; EQ-5D-3L - EuroQol Five Dimension Three Levels; HUI - Health Utilities Index; N/A - Not applicable; SE - Standard error; TREAT-NMD - Translational Research in Europe- Assessment and Treatment of Neuromuscular Disorders; UK - United Kingdom; USA – United States of America.

B.3.4.4. Adverse reactions

Utility decrements were applied to each acute event, moderate to severe AESI and comorbidity within the model and, applied per cycle for a set duration. The decrements and duration estimates used in the analysis are presented in Table 56 and Table 57 for moderate to severe AESIs and acute events, respectively.

Table 56: Utility decrements and duration estimates by adverse event of special interest

Moderate to severe AESI	Disutility	Duration (days) - Vamorolone	Duration (days) - SoC	Duration (days) – No treatment	Source
Weight gain	0.05	126	126	126.00	An ICER submission for DMD assumed a 0.05 disutility[101] which has applied for the duration of average weight increase adverse event in the VISION-DMD.[4]
Behavioural issues	0.12	182.63	182.63	182.63	Disutility calculated from de Kinderen et al. for behaviour issues, specifically for irritability and aggression in a paediatric population for epilepsy.[102] Assumed to last 6 months as a minimum duration discussed from a clinical expert.
Cushingoid effects	0.056	29.00	106.00	29.00	A disutility for impaired physical appearance has been applied from NICE submission HST14,[103] this has been applied for the duration of average cushingoid adverse event in VISION-DMD.
Immune supressed/infection	0.142	4.00	7.50	8.00	URTI was the most common infection which has been assumed to represent this event. Sullivan et al. 2011[104] noted a 0.142 disutility for the duration of average URTI adverse event in VISION-DMD.[4]
GI symptoms	0.020	365.00	365.00	365.00	Hvidberg et al. 2023. Assumed to last a year as a long-term event. [105]
Diabetes	0.030	365.00	365.00	365.00	Hvidberg et al. 2023, assumed to last a year as a long-term event.[105]
Skin/Hair change	0.056	365.00	365.00	365.00	A disutility for impaired physical appearance has been applied from NICE submission HST14[103] to capture hirsutism arising as part of skin and hair changes. This was assumed to last 1 year.
Stunted growth	0.056	365.00	365.00	365.00	A disutility for impaired physical appearance has been applied from NICE submission HST14[103] to capture the impact of short stature. This was assumed to last 1 year.

Abbreviations: AE – Adverse event of special interest; DMD – Duchenne muscular dystrophy; GI – Gastrointestinal; ICER – Incremental cost-effectiveness ratio; LTE – Long-term extension; N/A – Not available; SoC – Standard of care; URTI – Upper respiratory tract infection.

Table 57: Utility decrements and duration estimates by acute event

AE	Disutility	Duration (days) - Vamorolone	Duration (days) - SoC	Duration (days) – No treatment	Source
Diarrhoea	0.047	3.50	2.50	1.00	Sullivan et al. 2011. Applied for the duration of average diarrhoea adverse event in the LTE.[104] for the duration of average diarrhoea adverse event in VISION-DMD.[4]
Vomiting	0.095	1.80	1.00	2.50	Hagiwara et al. 2018. Applied for the duration of average vomiting adverse event in the VISION-DMD.[4]
Pyrexia	0.0297	3.80	2.50	3.30	Sullivan et al. 2011. Applied for the duration of average pyrexia adverse event in the VISION-DMD.[4]
Cough	0.046	4.50	15.00	7.00	Doyle et al. 2008.[106]Applied for the duration of average pyrexia adverse event in the VISION-DMD.[4]

Abbreviations: AE – Acute event; DMD – Duchenne muscular dystrophy; LTE – Long-term extension; SoC – Standard of care.

B.3.4.5. Health-related quality of life data used in the cost-effectiveness analysis

In addition to the Landfeldt et al study found in the SLR, a burden of illness (BOI) study, informed by a Delphi panel, collected HRQL data for patients and caregivers using a preference-based measure as part of Project HERCULES. The NICE reference case hierarchy states a preference for public preferences using a choice-based method.[95]

The BOI study is informed by patients and carers based in the UK and is therefore suitable for UK HTA submission.[107] As discussed in Section 0, despite EQ-5D data being collected during the VISION-DMD trial,[4] the scale was found to be lacking in sensitivity to nuances of DMD, a common issue when assessing HRQL in DMD patients, as supported by the findings in Powell et al.[51] Subsequently, the values selected for patients in the base case in the model adaptation are the DMD-QoL values from the BOI study.[107] The DMD-QoL scale was created by Project HERCULES specifically to measure the intricacies specific to utility for both patients and caregivers in DMD. The utilities from the DMD-QoL scale are based on the health state and not age, however, functionality will be added into the current model to allow for age-adjusted utilities as per the NICE reference case.[95]

Based on the BOI study, the majority of patients reported receiving assistance whether informally through a family member or friend (64%) or professional care (7%). Due to this, caregiver utilities have also been included within the model and are applied individually based on health state. The utilities obtained from the BOI study and Landfeldt et al. have been inverted to reflect a progressive disutility for caregivers as a patient progresses through the health states, using the Early ambulatory state as an anchor. This anchoring allows for accurate representation of the impact of patient progression on caregivers, rather than having additive health state utilities for caregivers. The BOI utilities data lacked data for health states 5, 6 and 7 and so were substituted with the utility values reported in Landfeldt et al. However, due to the inclusion of Landfeldt et al. data. the conversion of the BOI utilities to disutilities led to utility gains for carers during health states 5,6 and 7 which lacked face validity. Utility values for carers were therefore taken from Landfeldt et al. in the base case for all

health states. Disutilities are applied regardless of patients age and assumed to be one caregiver per-patient in the current model. The option to model multiple caregivers in the adapted model is evaluated through a scenario analysis. In this instance, all caregivers are assumed to have the same disutility per health state.

The health state utility values (HSUVs) obtained from the BOI study[107] are displayed in Table 60. The inverted disutility values obtained from the Landfeldt et al. and BOI study are displayed in Table 59. Any values unavailable from the BOI study remain as Landfeldt et al. values,[89] as used in the original Project HERCULES model (Table 59). A scenario will be conducted using Landfeldt et al. values exclusively.

Table 58: BOI utility values

Ambulatory class	DMD-QoL patient utility value	DMD-QoL caregiver utility value
Early ambulatory	N/A	0.55 (0.14)
Late ambulatory	0.49 (0)	0.41 (0)
Transfer	0.38 (0.1)	0.48 (0)
HTMF, no ventilation	0.54 (0.19)	0.63 (0)
No HTMF, no ventilation	0.51 (0.05)	N/A*
HTMF, night-time ventilation	0.53 (0.16)	N/A*
No HTMF, night-time ventilation	0.52 (0.15)	N/A*
Full-time ventilation	0.33 (0.04)	0.36 (0.19)

Abbreviations: BOI – Burden of illness; DMD-QoL – Duchenne muscular dystrophy quality of life; HTMF - Hand-to-mouth function; N/A – Not applicable; SE - Standard error.
*Data for health states 'no HTMF, no ventilation' to 'no HTMF, night-time ventilation' were not reported for the DMD-QoL caregiver utility due to limited sample in the BOI study. In the absence of data for these health states, data for these health states were taken from the caregiver utilities reported in Landfeldt.

Table 59: Landfeldt et al. utility values

Ambulatory class	Patient utilities	Caregiver utilities
Early ambulatory	0.699	0.86
Late ambulatory	0.607	0.84
Transfer	0.607	0.78
HTMF, no ventilation	0.224	0.78
No HTMF, no ventilation	0.224	0.78
HTMF, night-time ventilation	0.224	0.78
No HTMF, night-time ventilation	0.146	0.81

Full-time ventilation	0.146	0.81

Abbreviations: HTMF - Hand-to-mouth function.

Table 60: Caregiver disutilities in the model

Ambulatory class	Caregiver disutilities	
	BOI	Landfeldt et al.
Early ambulatory	0	0
Late ambulatory	-0.14	-0.02
Transfer	-0.07	-0.08
HTMF, no ventilation	0.08	-0.08
No HTMF, no ventilation	0.23	-0.08
HTMF, night-time ventilation	0.23	-0.08
No HTMF, night-time ventilation	0.26	-0.05
Full-time ventilation	-0.19	-0.05

Abbreviations: BOI – Burden of illness; HTMF – Hand-to-mouth function.

B.3.4.5.1. Behavioural issues disutility

As described in Section B.1.3, caregiver disutility specific to adverse events have been included within the analysis to display the detrimental impact which steroidal-related adverse events can have on a caregiver. Disutility was applied in relation to a patient experiencing behavioural issues, which has been documented within the literature via caregivers' utility being directly associated with their perception of the patient's mental status (Table 61).[108]

Table 61: Carer disutility and duration associated with behavioural issues

Disutility	Source	Duration	Source
0.11	HST22[108]	1 year	Assumption based off ethnographic research on the severe burden on carer. The impact was assumed to be long-term and was therefore set to last a full year.

B.3.4.5.2. Fractures

To capture the increasing severity of fractures, as described in Section 0, the disutility associated with fractures also increases as DMD progresses. The severity for the placebo arm is assumed to be in line with vamorolone, as bone density will not have been affected for these patients. Disutility values for spinal vertebral fractures and 'other fractures' (patella, tibia, fibula, ankle and femur) were sourced from Dipnall et al. 2021.[109] The paper looked at HRQL outcomes following injury in childhood with a

long-term follow-up of 24 months. A disutility for vertebral column fractures was used and an average of fractures for patella, tibia, fibula or ankle and fractures of the femur was used for the other fractures' disutility; these can be seen in Table 62. Long bone fractures can lead to permanent loss of ambulation due to DMD patients' reduced ability to recover and from muscle loss stemming from the temporary loss of ambulation.[110] The impact of fractures on ambulation is not captured in the model, therefore this may be a conservative approach as the model may not capture the true burden of long bone fractures.

The model includes the functionality for varying utilities by health state and treatment arm, but despite papers suggesting increased morbidity in fractures for corticosteroids due to thinner, weaker bones reducing the body's ability worse remodel bones, no specific data was found to use in the model.[111–114]

Table 62: Disutility associated with fracture severity

Spinal vertebral fractures	Other fractures	Duration
-0.05	-0.065	24 months

B.3.4.5.3. Scoliosis

The disutility associated with spinal surgery is displayed in Table 63. The disutility associated with spinal surgery is applied for the duration of one year.

Table 63: Comorbidities disutilities

Event	Disutility	Duration	Source
Spinal fusion surgery	-0.07	1 year	Disutility: Matza et al 2015[115] Duration: Assumption

B.3.4.9. Summary of utilities in the model

Table 64 summarises the utility values used in the economic analysis.

Table 64: Summary of utility values used in the economic analysis

State	Utility value: mean (SD)	95% confidence interval	Reference	Justification
HSUVs – BOI patient				
Early ambulatory	0.70	(0.63-0.77)	BOI study 2022[107]	The BOI study is the most up to date data source available that corresponds directly to the health states already included within the model. The study was conducted as part of the same Project HERCULES model and includes data obtained directly from the patients.
Late ambulatory	0.49	(0.43-0.55)		
Transfer	0.38	(0.35-0.41)		
HTMF, no ventilation	0.54	(0.51-0.57)		
No HTMF, no ventilation	0.51	(0.48-0.54)		
HTMF, night-time ventilation	0.53	(0.50-0.56)		
No HTMF, night-time ventilation	0.52	(0.50-0.54)		
Full-time ventilation	0.33	(0.31-0.35)		
HSUVs – caregiver disutilities				
Early ambulatory	0	N/R	BOI study 2022[107]	The BOI study is the most up to date data source available that corresponds directly to the health states already included within the model. The study was conducted as part of the same Project HERCULES model and where available, the caregiver utilities have been used in the base case.
Late ambulatory	-0.14	N/R		
Transfer	-0.07	N/R		
HTMF, no ventilation	0.08	N/R		
No HTMF, no ventilation	0.23	N/R	Landfeldt et al 2017[89]	Where BOI values were unavailable, Landfeldt et al was deemed the most appropriate next source of utilities. These values correspond directly to the model health states and have been accepted for use in previous submissions in DMD.
HTMF, night-time ventilation	0.23	N/R		
No HTMF, night-time ventilation	0.26	N/R		
Full-time ventilation	-0.19	N/R	BOI study 2022[107]	The BOI study is the most up to date data source available that corresponds directly to the health states already included within the model. The study

State	Utility value: mean (SD)	95% confidence interval	Reference	Justification
				was conducted as part of the same Project HERCULES model and where available, the caregiver utilities have been used in the base case.
Adverse event disutility				
Weight gain	0.05	N/R	ICER[101]	Value based on ICER submissions for DMD.
Behavioural issues	0.12	N/R	De Kinderen et al 2016[102]	Disutility calculated from de Kinderen et al. for behaviour issues, specifically for irritability and aggression in a paediatric population for epilepsy.
Cushingoid effects	0.056	N/R	HST14[103]	Value from a previous NICE submission, HST14, for impaired physical appearance. This value was based on several conditions including excessive facial hair, skeletal facial features, severe body asymmetry. This is seen to adequately captures cushingoid facial features.
Immune suppressed/infection	0.142	N/R	Sullivan et al 2011[104]	URTI was the most common infection which has been assumed to represent this event. Sullivan et al. 2011 noted a 0.142 disutility for the duration of average URTI adverse event in the LTE.
GI symptoms	0.020	N/R	Hvidberg et al. 2023.[105]	EQ-5D data based on chronic conditions and health risks.
Diabetes	0.030	N/R	Hvidberg et al. 2023[105]	EQ-5D data based on chronic conditions and health risks.
Skin/Hair change	0.056	N/R	HST14[103]	Value is from a previous NICE submission, HST14, for impaired physical appearance. This value was based on several conditions including excessive facial hair, skeletal facial features, severe body asymmetry. This is captures hirsutism which arising during skin and hair adverse event for those with DMD.
Stunted growth	0.056	N/R	HST14[103]	Value is from a previous NICE submission, HST14, for impaired physical appearance. This value was based on several conditions including excessive

State	Utility value: mean (SD)	95% confidence interval	Reference	Justification
				facial hair, skeletal facial features, severe body asymmetry. This is seen to adequately captures the impact suffered from those with short stature due to DMD.
Acute event disutility values				
Diarrhoea	0.047	N/R	Sullivan *et al* 2011[104]	Diarrhoea disutility applied for the duration of average diarrhoea adverse event in the LTE.
Vomiting	0.095	N/R	Hagiwara et al. 2018[116]	Vomiting disutility applied for the duration of average vomiting adverse event in the LTE.
Pyrexia	0.0297	N/R	Sullivan *et al* 2011[104]	Pyrexia disutility applied for the duration of average pyrexia adverse event in the LTE.
Cough	0.046	N/R	Doyle et al. 2008[106]	Assumed similar to pyrexia, so the disutility for cough is applied for the duration of average pyrexia adverse event in the LTE.
Comorbidities				
Spinal vertebral fractures	0.05	N/R	Dipnall *et al.* 2021[109]	Dipnall et al. assessed the outcomes following injury in childhood, reflecting disutilities directly applicable to the intended population. These outcomes were available specifically for spinal and other fractures, categorised in the same way as the model.
Other fractures	0.04	N/R		
Spinal surgery	0.07	N/	Matza et al 2013[115]	Utilities based on skeletal-related events, specifying the disutility obtained specifically from bone-related surgery.
Caregiver disutility				
Behavioural issues	0.11	N/R	HST22[108]	Assumption based off ethnographic research on the severe burden on carer. The impact was assumed to be long-term and was therefore set to last a full year.

Abbreviations: BOI – Burden of illness; DMD – Duchenne muscular dystrophy; EQ-5D – EuroQol Five Dimensions; GI – Gastrointestinal; HTMF – Hand-to-mouth function; HSUV – Health state utility values; ICER – Incremental cost-effectiveness ratio; LTE – Long-term extension; N/R – No result; URTI – Upper respiratory tract infection.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify studies reporting on the cost and resource use of patients with DMD. Full details of the process and methods used to identify and select the cost and resource use data relevant to the technology being evaluated are presented in Appendix I.

The SLR identified 15 cost and resource use studies from a UK perspective for patients with DMD.

Consistent with the studies identified in the SLR, the following cost categories were included in the model:

- Drug acquisition and administration costs applied for the duration of primary and subsequent treatment,
- Medical resource use costs.

For cost inputs, an NHS and PSS perspective was adopted. Unit costs of drug acquisition, administration, resources use, and AE management were based on standard costing sources.

B.3.5.1. Intervention and comparators' costs and resource use

Monthly treatment costs for vamorolone and SoC were calculated to align with the model cycle length. Dosing information for SoC was sourced from DMD guidelines[117] and costs were sourced from the BNF[118-119]. No administration costs were considered since vamorolone, and steroids are both taken orally. The anticipated list price (excluding VAT) for 100ml of 40mg/ml of vamorolone is £4,585.87. A simple Patient Access Scheme (PAS) discount of [redacted]% is applied in the model, pending approval at the time of writing. For the SoC arm, the proportion of patients were split across prednisone and deflazacort which was based of the BOI study with 84% on prednisone.[107] Due to treatment discontinuation and down-titration being captured separately (see Section 0), compliance was assumed to be 100% while patients remain on-treatment. All input data and the resulting total cost per cycle for each arm are described in Table 65.

Table 65: Drug package price and cost per cycle

Treatment	Dosage strength	Pack size/ vial volume	Dosing pattern	Administration route	Cost per pack at list price (£)	SoC weighting split	Cost per monthly cycle (£)	Sources
Intervention								
Vamorolone	6.0 mg/kg	100ml 40mg/ml	Daily	Oral	£4,585.87	N/A	• With PAS = [redacted]/kg • List price = £209.37/kg	VISION-DMD (Santhera data on file)[4]
	4.0 mg/kg				£4,585.87		• With PAS = [redacted]/kg • List price = £139.58/kg	
	2.0 mg/kg				£4,585.87		• With PAS = [redacted]/kg • List price = £69.79/kg	
SoC								
Prednisone	0.75 mg/kg	60 tablets 6mg	Daily	Oral	£15.82	84%	£0.67/kg	BNF Prednisolone[118]
	0.53 mg/kg	60 tablets 6mg	Daily	Oral	£15.82	Based on proportion lowering dose	£0.18/kg	BNF Prednisolone[118]
Deflazacort	0.9 mg/kg	28 tablets 10mg	Daily	Oral	£9.70	16%	£0.48/kg	BNF Deflazacort[119]
	0.64mg/kg	28 tablets 10mg	Daily	Oral	£9.70	Based on proportion lowering dose	£0.13/kg	BNF Deflazacort[119]

Abbreviations: Kg – Kilogram; Mg – Milligram; Ml – Millilitres; N/A – not applicable; SoC – Standard of care.

B.3.5.2. Health state costs and resource use

Health state costs comprising of medical and non-medical costs were sourced from the BOI study and displayed in Table 66. The BOI study, steered by Project HERCULES, is a retrospective, cross-sectional, multi-site prevalence based study involving physicians, patients and carers to capture detailed resource utilisation data. Costs included not only all health-related items, but also non-health and indirect costs accruing to patients and their families.

For this submission, only direct medical and non-medical costs were taken from the BOI study. Additionally, corticosteroid and non-corticosteroid costs were removed as these are considered separately in the analysis, and professional caregiver costs were removed as these costs will be borne by individuals as opposed to the health service. Direct medical costs, therefore, include test and procedures, medical devices, consultations, and hospitalisations while direct non-medical costs are inclusive of home alterations, over the counter (OTC) medications, transport, transfer payment, alternative therapy, and other non-medical costs. Disaggregated costs are displayed in Table 67 and Table 68 for medical and non-medical costs, respectively.

Health state costs are the same across all arms as they are unrelated to treatment. Differences between arms regarding health states costs can only arise based on how quickly an individual progresses through the health state. All costs were inflated to 2023 costs from 2020 using the OECD inflation indices.[120]

Table 66: List of health states and associated costs in the economic model

Health states	Total Value	Source
Early ambulatory	£7,679.96	BOI study[96], inflated to 2023 from 2020 using OECD.[120]
Late ambulatory	£3,390.77	
Transfer	£3,625.18	
HTMF, No ventilator	£2,472.27	
No HTMF, No ventilator	£3,507.11	
HTMF, Night ventilator	£7,837.81	
No HTMF, Night ventilator	£7,771.39	
Full ventilator	£12,579.16	

Abbreviations: BOI – Burden of illness; HTMF – Hand-to-mouth function; OECD - Organisation for Economic Cooperation and Development.

Table 67: Disaggregated direct medical costs per health states from BOI study (inflated to 2023 values)

Cost category	Early ambulatory	Late ambulatory	Transfer	HTMF, no ventilator	No HTMF, no ventilator	HTMF, night ventilator	No HTMF, night vent	Full-time ventilation
Tests and medical procedures	£2,596.16	£1,386.27	£737.70	£284.30	£1,939.84	£1,642.70	£1,370.81	£1,645.29
Medical devices	£1,048.93	£360.14	£1,333.85	£670.54	£80.24	£5,059.34	£5,227.93	£6,907.34
Consultations	£1,186.06	£972.84	£1,061.73	£917.16	£949.18	£886.19	£571.77	£914.40
Hospitalisations	£0.00	£6.69	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00

Abbreviations: HTMF – Hand-to-mouth function.

Table 68: Disaggregated direct non-medical costs per health states from BOI study (inflated to 2023 values)

Cost category	Early ambulatory	Late ambulatory	Transfer	HTMF, no ventilator	No HTMF, no ventilator	HTMF, night ventilator	No HTMF, night vent	Full-time ventilation
Home alterations	£169.14	£64.72	£103.56	£262.34	£48.55	£8.28	£18.12	£0.26
OTC medication	£54.54	£229.90	£32.80	£20.71	£40.78	£22.78	£31.07	£569.56
Transport	£127.72	£0.00	£75.94	£103.56	£3.11	£36.24	£19.42	£2,446.52
Transfer payments	£104.25	£258.89	£155.33	£213.67	£445.43	£182.26	£532.28	£95.79
Alternative therapy	£942.36	£103.56	£124.27	£0.00	£0.00	£0.00	£0.00	£0.00
Other non-medical costs	£1,449.79	£7.77	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00

Abbreviations: HTMF – Hand-to-mouth function.

B.3.5.3. Adverse reaction unit costs and resource use

The acute events and moderate to severe AESI used within the model are described fully in B.3.4.4. Adverse reactions. Given that the medical costs reported in Landfeldt et al. 2017 already include the cost of hospitalisation, no further costs were applied for those patients undergoing hospitalisation due to acute respiratory failure or pneumonia.[89] Resource use associated with each acute event was validated with a clinical expert in DMD. The costs associated with moderate to severe AESI and acute events are displayed in Table 69 and Table 70. All costs were inflated to 2022/23 costs using the OECD CPI index.[120]

Table 69: Costs associated with moderate to severe AESI in the model

Adverse reactions	Items	Value	Source
Weight gain	4.5 Dietician appointments based on clinical opinion of 3-6 dietician appointments.	£450 (4.5 x £100)	PSSRU 2022[121]
	No medical intervention, often managed by down-titration.		
Behavioural issues	6 psychologist community therapy sessions.	£378 (6 x £63)	PSSRU 2012 inflated via OECD index [122]
Cushingoid effects	1 GP visit (then managed through regular DMD check-ups).	£41	PSSRU 2022[121]
	No medical intervention, NHS recommends management through down-titration or discontinuation.[123]		
Immune supressed/infection	Based off URTI as the most common infection, 1 GP visit.	£41	PSSRU 2022[121]
GI symptoms	Assumed equal to the mean direct healthcare cost of management of IBS Rome III in UK. Includes all appointments, tests, ED visits and medication.	£474	Goodoory 2022[124]
Diabetes	Paediatric diabetes year of care.	£3,189	NHS tariff costs 2021/22[125]
Skin/Hair change	1 GP visit.	£41	BNF and The Royal Children's Hospital Melbourne[126,127]
	2 x 15g steroid cream for skin management. Dermacort hydrocortisone 0.1% cream Marlborough Pharmaceuticals Ltd.	£6 (2 x £2.83)	
Stunted Growth	Cost of growth hormone therapy for 1 year based on lowest dosing of 0.17mg/kg once a week. (£106.35 for BNF Norditropin FlexPro 5mg/1.5ml solution for injection pre-filled pens)	£6,451	BNF[128]

Abbreviations: AESI – Adverse events of special interest; BNF – British National Formulary; DMD – Duchenne Muscular Dystrophy; ED – Emergency Department; GI – Gastrointestinal; GP – General Practitioner; IBS – Irritable bowel syndrome; Kg – Kilogram; Mg – Milligram; NHS – National Health Service; OECD – Organisation for Economic Cooperation and Development; PSSRU – Personal Social Services Research Unit; UK – United Kingdom; URTI – Upper respiratory tract infection.

Table 70: Costs associated with acute events in the model

Adverse reactions	Items	Value	Source
Diarrhoea	Self-management	£6.86	NHS recommendation is to self-management with paracetamol[129] plus 1/6 of patients requiring e-consultation; based on clinician input[121]
Vomiting	Self-management	£6.86	NHS recommendation is to self-management with paracetamol[129] plus 1/6 of patients requiring; based on clinician input[121]
Pyrexia	1 GP visit	£41.00	PSSRU 2022[121]
Cough	Self-management	£0.00	NHS recommendation is to self-management with paracetamol[130]

Abbreviations: GP – General Practitioner; NHS – National Health Service; PSSRU – Personal Social Services Research Unit.

Costs for spinal vertebral fractures and other fractures were sourced from the NHS reference costs 2021/2022 and the BNF. To capture 'other fractures' cost, a weighted average of fractures of the arm, hip, foot, and knee was taken for all severities. For the spinal vertebral costs, the cost for a vertebral column injury with an intervention was used since only symptomatic fractures are included within the model and treatment is recommended even for asymptomatic moderate to severe vertebral fractures.[16,35] A further cost for bisphosphonates treatment is included for vertebral fractures since they are indicative of high-risk fragility patients. This cost was applied to 60% of vertebral fractures to capture 6/10 boys with symptomatic vertebral fractures receiving intravenous bisphosphonate therapy in a study from Crabtree et al 2018.[131] Within these costs, there was treatment with Zoledronic acid at 0.05mg/kg every 6 months and the cost of an IV.[132] This was multiplied by the average length of treatment, 4.2 years. The fracture cost also included one DEXA scan from NHS reference costs 2021/2022 and, the cost of 50mg of hydrocortisone for moderate surgical stresses to combat lack adrenal in DMD boys due to chronic glucocorticoid use.[133] The IV cost for the emergency steroid use are assumed to be captured with the NHS reference costs. The final costs used in the model can be seen in Table 71.

Table 71: Fracture costs

	Costs	Source
Other Fractures	£3,301.44	NHS reference costs. Weighted average of fractures of arm, hip, foot, and knee Codes: HE51H, HE51, HE41C, HE41D, HE31G, HE31C, HE21G, HE21D, HE11H, HE51G, HE51F, HE51B, HE31F, HE31B, HE21F, HE21C, HE51D, HE51E, HE51A, HE41A, HE31D, HE21E, HE21B, HE11F, HE11E, HE11C, HE11D, HE31E, HE11G. Single DEXA scan from NHS reference cost 2021/2022
Spinal vertebral fractures	£15,167.27	NHS reference costs. Vertebral Column Injury with Interventions HC20H Zoledronic acid 4mg/ml infusion bag BNF[134] Single Plasma Exchange or Other Intravenous Blood Transfusion, 18 years and under SA44B Single DEXA scan from NHS reference cost 2021/2022

Abbreviations: BNF – British National Foundry; NHS – National Health Service.

The cost implications from experiencing scoliosis were captured through spinal fusion surgery events, shown below in Table 72 and applied as a one-off cost within the model.

Table 72: Scoliosis costs in the economic model

Resource	Units per event	Cost per unit	Source
Spinal surgery cost	1	£25,259.63	In line with HST22.[108] Cost updated to NHS reference costs 2021/2022, a weighted average of complex spinal reconstructive procedures CC4+. Codes HC52A and HC52B.
Surgery follow-up	2	£5,174.82	In line with HST22.[108] Cost updated with NHS reference costs 2021/2022 for scoliosis or other spinal deformity CC3+. Code HC26D.
Indirect	1	£23,172.91	Cost taken from HST22[108] and updated to 2022 via the OECD inflation index.
Total		**£58,782.19**	

Abbreviations: NHS – National Health Service; OECD – Organisation for Economic Cooperation and Development.

B.3.6. Severity

Based on the QALY shortfall calculator published by Schneider et al., the estimated absolute QALY shortfall of the cohort is 18.02 years, while the proportional QALY shortfall of the cohort is 72.37% which therefore includes the 1.7x multiplier as

described in Table 73.[135] This supports the application of the 1.7x multiplier per QALY gained to this appraisal.

Table 73 details the factors used for the QALY shortfall calculator. Patient characteristics were considered consistently with the base case CEM and reported a mean age at baseline of 4.1 years and a 100% male population. Table 74 outlines the health state utility values and associated undiscounted life years spent in each health state for DMD patients receiving SoC.

Table 75 presents the results of the QALY shortfall analysis; the general population of the same age without DMD would be expected to accrue 24.90 discounted QALYs throughout their lifetime, compared to 6.88 for patients with DMD under current SoC in the UK. The absolute QALY shortfall is 18.02, meaning vamorolone is eligible for the 1.7x severity modifier. Note, the QALY shortfall analysis only considers patient associated QALYs for SoC patients; given the substantial impact that DMD has on carers, it may be reasonable to include caregiver disutilities in the analysis. A scenario presenting this analysis is shown in the table.

Table 73: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution	100% male	B.3.2.1
Starting age	4.1 years	B.3.2.1
Discount rate	3.5%	B.3.2.2
Remaining LY of population	UK life tables[136]	Life tables England 2017-2019 (pooled)
Remaining QALY of population	UK population utility norms[137–139]	• Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study • Health state profiles: EQ-5D-3L from the Health Survey for England 2014 • Model: ALDVMM by Hernandez Alava, et al. 2022
Health state utility values	BOI study values	B.3.4.9
Adverse reaction disutilities	Multiple sources	B.3.4.4
Fracture disutility	Dipnall et al. 2021[109]	B.3.4.5.2
Scoliosis disutility	Matza et al. 2015[115]	B.3.2.5.3

Table 74: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Early ambulatory	0.70	3.90
Late ambulatory	0.49	2.83
Transfer	0.38	1.27
HTMF, no ventilator	0.54	1.61
No HTMF, no ventilator	0.51	2.20
HTMF, night ventilator	0.53	2.12
No HTMF, night vent	0.52	1.76
Full-time ventilation	0.33	12.92

Table 75: Summary of QALY shortfall analysis

Analysis	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Base case: patient impact only	24.90	6.88	18.02
Scenario: including caregiver disutilities	24.90	5.57	19.33

B.3.7. 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. There is an abundance of qualitative data on steroid burden to patients and carers but limited quantitative data for long-term steroid use effects creating uncertainty around the efficacy and safety. Furthermore, heterogeneous steroid dosing patterns complicate evidence interpretation.

In addition, many key outcomes in DMD, such as fractures and bone health, manifest years into the future, often outside the typical timeframe of a clinical trial. This requires a reliance on assumptions and clinician experience to assess how early biomarkers can predict these future outcomes, potentially introducing uncertainties into the evidence.

The uncertainty in the model results was explored through extensive one-way sensitivity analysis (OWSA), probabilistic sensitivity analysis (PSA), and scenario analyses. In the OWSA, each variable was systematically increased and decreased based on 95% confidence intervals or published ranges. In the absence of data, the higher and lower values were calculated as ± 15% of the mean base case value. A number of scenario analyses were also performed to assess the impact of alternative assumptions and data sources which were not captured within the OWSA and PSA.

B.3.8. Managed access proposal

It is not anticipated that vamorolone is eligible for a managed access fund.

B.3.9. Summary of base case analysis inputs and assumptions

Summary of base case analysis inputs

A summary of the key parameters used in the CEM is presented in Table 76.

Table 76: Summary of variables applied in the economic model

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Model settings			
Weight data	VISION-DMD	N/A	0
Perspective	NHS PSS	N/A	0
Time horizon	50 years	Not modelled	0
Starting age in model (years)	4.1	N/A	0
Half-cycle correction	Yes	Fixed	0
Discount rate (cost and outcomes)	3.5%	Fixed	0
Probability per cycle of acute event – Vamorolone			
Diarrhoea	1.33%	Beta	0
Vomiting	2.75%		
Pyrexia	0.00%		
Cough	1.33%		
Probability per cycle of acute event – Glucocorticoids			
Diarrhoea	1.20%	Beta	0
Vomiting	1.20%		
Pyrexia	1.20%		
Cough	1.83%		
Bone health			

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Other fractures probability per cycle – varied by health state and arm			
Vamorolone	0.05% - 0.33%	Beta	
SoC	0.00% - 0.79%		
No Treatment	0.00% - 0.33%		
Spinal vertebral fractures probability per cycle – varied by health state and arm			
Vamorolone	0.00% - 0.56%	Beta	
SoC	0.00% - 1.36%		
No Treatment	0.00% - 0.56%		
Proportion receiving spinal surgery			
Vamorolone	10.00%	Beta	
SoC	10.00%		
No Treatment	90.00%		
Health-related quality of life parameters			
Health state utilities			
Early ambulatory	0.70	Beta	0
Late ambulatory	0.49		
Transfer	0.38		
HTMF, no ventilation	0.54		
No HTMF, no ventilation	0.51		
HTMF, night-time ventilation	0.53		
No HTMF, night-time ventilation	0.52		
Full-time ventilation	0.33		
Caregiver health-related quality of life parameters			
Early ambulatory	0.00	Beta	B.3.4.5
Late ambulatory	-0.02		
Transfer	-0.08		
HTMF, no ventilation	-0.08		
No HTMF, no ventilation	-0.08		
HTMF, night-time ventilation	-0.08		
No HTMF, night-time ventilation	-0.05		
Full-time ventilation	-0.05		
Disutilities - AESI			
Weight gain	0.025	Beta	0
Behavioural issues	0.011		
Cushingoid effects	0.025		
Immune supressed/infection	0.142		
GI symptoms	0.02		
Diabetes	0.03		
Skin/Hair change	0.03		

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Stunted growth	0.00		
Behavioural issues caregiver	0.11		B.3.4.5.1
Disutilities – Acute events			
Diarrhoea	0.047	Beta	0
Vomiting	0.095		
Pyrexia	0.297		
Cough	0.046		
Bone health – Disutilities			
Spinal fusion surgery	-0.07	Beta	B.3.4.5.2
Spinal vertebral fractures	0.05		
Other fractures	0.065		B.3.4.5.3
Event duration			
AESI event durations (days)			
Weight gain	126.00	Gamma	B.3.4.4
Behavioural issues	182.63		
Cushingoid effects – vamorolone	29.00		
Cushingoid effects - SoC	106.00		
Cushingoid effects – no treatment	29.00		
Immune supressed/infection - vamorolone	4.00		
Immune supressed/infection - SoC	7.50		
Immune supressed/infection – no treatment	4.00		
GI symptoms	365.00		
Diabetes	365.00		
Skin/Hair change	365.00		
Stunted growth	365.00		
Acute event durations			
Diarrhoea – vamorolone	3.50	Gamma	B.3.4.4
Diarrhoea - SoC	2.50		
Diarrhoea – no treatment	1.00		
Vomiting – vamorolone	1.80		
Vomiting – SoC	1.00		
Vomiting – no treatment	2.50		
Pyrexia – vamorolone	3.80		
Pyrexia – SoC	2.50		
Pyrexia – no treatment	3.30		
Cough – vamorolone	4.50		
Cough - SoC	15.00		

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Cough – no treatment	7.00		
Bone health event durations			
Spinal fusion surgery	365.25	Gamma	B3..4.5.3
Spinal vertebral fractures	720.00		B.3.4.5.2
Other fractures	720.00		
Cost parameters			
Intervention and comparator costs per month			
Vamorolone	£136.30	Log-normal	0
Prednisone	£0.67		
Deflazacort	£0.20		
Adverse event of special interest costs			
Weight gain	£41.00	Log-normal	0
Behavioural issues	£514.00		
Cushingoid issues	£41.00		
Immune suppressed/infection	£41.00		
GI symptoms	£474.16		
Diabetes	£3,189.00		
Skin/Hair change	£51,98		
Stunted growth	£6,988.81		
Acute event costs			
Diarrhoea	£0.00	Log-normal	0
Vomiting	£0.00		
Pyrexia	£41.00		
Cough	£0.00		
Bone health costs			
Spinal fusion surgery	£58,782.19	Log-normal	B.3.5.3
Spinal vertebral fractures	£15,167.27		
Other fractures	£3,301.44		

Abbreviations: AESI – Adverse event of special interest; DMD – Duchenne muscular dystrophy; GI – Gastrointestinal; HTMF – hand-to-mouth function; N/A – Not available; NHS – National Health Service; PSS – Personal Social Services.

Assumptions

The assumptions included in the model are presented in Table 77.

Table 77: Model assumptions and justifications

Assumption	Justification
Model structure	
The model adaptation aligns with the SmPC, the average age of patients in the model is 4.1 years old (average age of diagnosis).	Reflects SmPC wording for vamorolone to reflect patients 4 years and above. Scenarios are included for 5.41 years old, to reflect ages 4 – 7 years in line with the VISION-DMD trial. There is no age cap to the model.
Patients enter the model adaptation in the early ambulatory state.	To reflect the young age patients are diagnosed and enter the model (4.1 years old), all patients are assumed to be in the early stages of DMD and are placed in the early ambulatory health state.
The weight of boys with DMD treated with vamorolone is assumed equal to that of the 50th percentile of boys in the general population.	Limited weight data for steroid and steroid-naïve patients were available. In lieu of this data, the 50th percentile was deemed the most consistent with the DMD-specific weight data that was available.
The risk of spinal surgery is assumed to remain constant across a treatment arm with patients not switching to a different rate when they discontinue or lower their dosing.	There are several causes that lead to the need to spinal surgery that cannot all be reversed upon switching/changing their treatment, such as spinal maturity, so patients' long-term treatment pathway has been assumed to define their risk of spinal surgery over their lifetime.
Clinical effectiveness	
It is assumed that the NHM is representative of vamorolone and optimal steroid dosing in the population of interest.	The NHM dataset is comprised of IPD from 11 international data sources, including NH studies, placebo arms of clinical trials and registry data; it is therefore assumed representative of the population and of limited bias. The NHM source data consists of 80% steroids users, however dosing regimens are unknown. Clinical validation confirmed the NHM should broadly reflect SoC in the UK.
DMD is progressive and patients cannot transition backwards.	This assumption aligns with the natural progression of the disease that once patients lose e.g. ambulation or respiratory function, they cannot regain it. Glucocorticoids work by slowing disease progression rather than curing the disease. It is therefore not possible to progress back through previous health states. This assumption was clinically validated.

Assumption	Justification
Patients may only transition to the next-severe health state.	The model uses a 1-month cycle, assumed to be a sufficiently short enough timeframe that patients would only transition one milestone at most. This assumption was clinically validated.
Within each health state, the probability of progression is constant.	Except for the transitions from 8A/8B to death, an exponential distribution (i.e., constant transition intensities) was used to fit the multi-state model for transitions. Initial consideration of the exponential distribution for all transitions led to an implausibly long length of stay in state 8A/8B. This was due to the long tails associated with the exponential distribution and a fixed mortality rate. Therefore, a piecewise exponential distribution was assumed for transitions from state 8A/8B to state 9 (death). Use of the piecewise exponential facilitated implementation of an increased rate of mortality after age 30 years in state 8A/8B.
The probability of death varies only by health state; not by treatment arm.	As treatment with vamorolone is not anticipated to impact mortality of DMD patients, the only impact on mortality within the model adaptation is varying mortality rates by health state.
Cost and resource use	
Health state costs capture the cost of cardiomyopathy.	The only way in which treatments can affect cardiomyopathy is by delaying the progression of disease, therefore costs are assumed to be captured within the health state costs.
The cost of progression is incurred at the point a patient enters the health state.	This ensures all patients entering the health state are accounted for regarding costs.
All patients with stunted growth receive growth hormone.	The standard practice for patients with stunted growth is to receiving growth hormone therapy in order to combat stunted growth. The additional cost of this therapy has been added to the SoC/glucocorticoid arm only, as vamorolone showed catch-up growth within VISION-DMD.
QoL inputs	
AEs specific to treatment only occur when the individual is on-treatment. If not on-treatment, AE rates are assumed to equal placebo data from VISION-DMD	VISION-DMD placebo AE rates were deemed appropriate when treatment is discontinued as patients will not be exposed to the toxicity of active treatment.
AEs occur at a constant rate between health states.	There is no variation anticipated between patients within the same health state.
Comorbidities may impact costs and QoL, but do not impact disease progression or mortality. It is assumed that the impact of scoliosis and cardiomyopathy is implicitly captured in the NHM.	The only way in which treatments can affect cardiomyopathy or scoliosis is by delaying the progression of disease, therefore costs and QoL are assumed to be captured implicitly within the NHM.

Assumption	Justification
The long-term impact of scoliosis and cardiomyopathy on utility is implicitly captured.	
Spinal fusion surgery does not occur in ambulatory patients.	Based on the literature and clinical opinion, spinal fusion surgery only occurs once a patient is no longer ambulatory.
The impact of spinal fusion surgery on HRQL can be represented as a one-off QALY loss.	Spinal fusion surgery is a singular procedure to be conducted once, therefore it has been modelling to reflect a one-off QALY loss to patients which undergo surgery.
Caregiver utilities, when selected, are applied regardless of patient age.	In line with the literature, patients with DMD require a caregiver from diagnosis through to non-ambulatory states.[140]
One caregiver is assumed within the model.	Due to limited data on the impact of having multiple caregivers, all caregivers are assumed to have the same utility values. A scenario considering two caregivers is included.
Disutilities for behavioural issues for patient and caregiver are assumed to last six months.	This AE is a long-term issue but due to its impact on QoL it is assumed individuals will down titrate to reduce behavioural issues and prevent it occurring over a longer period. Clinical validation indicated that behavioural issues would occur for a minimum of six months and generally be longer-term issues.
Disutilities for the adverse events GI symptoms, diabetes and skin/hair change are assumed to last a year.	These AEs are severe long-term conditions which are not easily managed so a full year has been assumed appropriate to capture this.

Abbreviations: AE - Adverse event; DMD - Duchenne muscular dystrophy; GI – Gastrointestinal; HRQL – Health-related quality of life; IBS – Irritable bowel syndrome; ICER – Incremental cost-effectiveness ratio; IPD – Individual patient level data; NH – Natural history; NHM – Natural history model; QALY – Quality-adjusted life year; QoL – Quality of life; SoC – Standard of care; TTSTAND - Time to stand from supine.

B.3.10. Base case results

B.3.10.1. Base case incremental cost-effectiveness analysis results

This section presents the base case results for the CEM comparing vamorolone to SoC in a population of DMD patients using both the PAS and list prices respectively.

The base case results are presented in Table 78 below for the confidential simple PAS discount of [redacted] for vamorolone as described in Section B.1.2. Vamorolone was associated with [redacted] incremental costs and 2.76 incremental QALYs, resulting in an ICER of [redacted] indicating that vamorolone is cost-effective at a threshold of £30,000 per QALY over a 50-year horizon.

The base case results are presented for the list price for vamorolone as described in Section B.1.2 in Table 79. Vamorolone was associated with [redacted] incremental costs and 2.76 incremental QALYs, resulting in an ICER of [redacted]

Disaggregated base case results are presented in Appendix J.

The net health benefit is displayed in Table 80 and Table 81 for the PAS and list prices respectively. The NHB of vamorolone is [redacted] at a WTP threshold of £30,000 based on the PAS price, implying that overall population health would be increased as a result of introducing vamorolone when considering the proposed PAS.

Table 78: Base case results (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
SoC	[redacted]	28.32	5.57	-	-	-	-
Vamorolone	[redacted]	28.71	7.19	[redacted]	0.39	2.76	[redacted]

Abbreviations: ICER - Incremental cost-effectiveness ratio; LYG - Life years gained; QALY - Quality-adjusted life year.

Table 79: Base case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
SoC	[redacted]	28.32	5.57	-	-	-	-
Vamorolone	[redacted]	28.71	7.19	[redacted]	0.39	2.76	[redacted]

Abbreviations: ICER - Incremental cost-effectiveness ratio; LYG - Life years gained; QALY - Quality-adjusted life year.

Table 80: Net health benefit (PAS price)

Technologies	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
SoC	[redacted]	-	-	-	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER - Incremental cost-effectiveness ratio; LYG - Life years gained; NHB – Net health benefit; QALY - Quality-adjusted life year.

Table 81: Net health benefit (list price)

Technologies	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
SoC	[redacted]	-	-	-	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER - Incremental cost-effectiveness ratio; LYG - Life years gained; NHB – Net health benefit; QALY - Quality-adjusted life year.

B.3.11. Exploring uncertainty

B.3.11.1. Probabilistic sensitivity analysis

PSA was performed to explore the uncertainty around key model inputs. PSA was conducted by varying these inputs simultaneously by assigning distributions and recording the mean model results. A total of 1,000 PSA iterations were run in order to obtain a stable estimate of the mean model results.

The following parameters were kept fixed in the PSA: time horizon, discount rate for costs and outcomes, cycle length, average age and starting distribution. A summary of the variables used within the economic model is detailed in Table 76. Normal distributions were used to vary weight, multivariate log-normal distributions were used to vary the transition intensity for the NHM, log-normal distributions were for hazard ratios, beta distributions were used for probabilities of AESI and acute events and disutilities and gamma distributions were used for disutility durations and costs.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) was also plotted.

PSA results of vamorolone versus SoC are presented in Table 82 and Table83 for the PAS and list prices respectively.

The mean total costs and QALYs as predicted by the PSA results are similar compared to the deterministic base case results demonstrating the robustness of the base case results (Table 78 and Table 79 for the PAS and list prices, respectively). Patients receiving vamorolone accrued 7.37 QALYs at a cost of [redacted] based on the PAS price. Patients receiving SoC accrued 5.75 QALYs at a cost of [redacted] based on the PAS price analysis. Incremental QALYs were adjusted using the severity modifier. This resulted in a probabilistic ICER of £[redacted]. Probabilistic results for the list price are presented in Table83.

The ICEP presented in Figure 25 shows that when considering the vamorolone proposed PAS, all of the iterations fell in the north-east where vamorolone is more costly and more effective. Considering the proposed PAS, at a threshold of £30,000/QALY, the probability of vamorolone being cost-effective compared to SoC is [redacted] as shown by the CEAC presented in Figure27. The CEAC results should be interpreted with caution and appear skewed. This is because the model runs simulations based on the total costs and QALYs which cannot include the QALY severity modifier. As such, CEAC results underestimate the true cost-effectiveness of vamorolone. The corresponding results using the anticipated list price are presented in Figure26 and Figure28 respectively.

Table 82. PSA results with proposed PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	5.75	-	-	-
Vamorolone	[redacted]	7.37	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table83. PSA results with proposed list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	5.74	-	-	-
Vamorolone	[redacted]	7.37	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 25. Incremental cost-effectiveness plane with PAS price

Abbreviations: PAS, patient access scheme; SoC, standard of care.

Figure26. Incremental cost-effectiveness plane with list price

Abbreviations: SoC, standard of care.

Figure27. Cost-effectiveness acceptability curve with PAS price

Abbreviations: PAS, patient access scheme

Figure28. Cost-effectiveness acceptability curve with list price

Abbreviations: SoC, standard of care.

B.3.11.2. Deterministic sensitivity analysis

OWSA was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower CIs sourced from literature in the first instance or calculated from the pre-specified probabilistic distributions assigned to each parameter as an alternative. Where the standard error was unavailable to calculate upper and lower CIs, this was assumed to be 15% of the mean value. The mean values for the parameters included in the OWSA are shown in Table 76.

A tornado diagram is presented to illustrate the level of uncertainty considering the ICER. A tornado diagram is presented for vamorolone versus SoC considering the proposed vamorolone PAS in Figure 29. The top 10 most sensitive parameters are presented in Abbreviations: BOI, burden of illness study; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme; SoC, standard of care

Table 84 when considering the proposed PAS.

The OWSA results demonstrated the model was most sensitive to health state costs for the early ambulatory and full-time ventilation health states, in addition to the caregiver disutility applied to behavioural issues.

Figure 29: Tornado plot of OWSA results (incremental costs) for vamorolone vs SoC (proposed PAS price)

Abbreviations: BOI, burden of illness study; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme; SoC, standard of care

Table 84: OWSA results (incremental costs) for vamorolone vs SoC (proposed PAS price)

Parameter name	Lower incremental costs	Upper incremental costs
Direct costs by health state (BOI) - SoC: 8 - full-time ventilation	[redacted]	[redacted]
Direct costs by health state (BOI) - Vamorolone: 8 - full-time ventilation	[redacted]	[redacted]
Direct costs by health state (BOI) - Vamorolone: 1 - early ambulatory	[redacted]	[redacted]
Direct costs by health state (BOI) - SoC: 1 - early ambulatory	[redacted]	[redacted]
Behavioural issues: caregiver disutilities	[redacted]	[redacted]

Parameter name	Lower incremental costs	Upper incremental costs
Behavioural issues (caregiver): Duration of event (days)	[redacted]	[redacted]
Stunted growth costs		
Vamorolone hazard ratio: To state 2 - Late ambulatory		
Vamorolone - Average weight: Age 4		

Abbreviations: BOI, burden of illness study; OWSA, one-way sensitivity analysis; PAS, patient access scheme; SoC, standard of care

A tornado diagram is presented for vamorolone versus SoC in Figure 30 using the list price for vamorolone. The top 10 most sensitive parameters are presented in Table 85 when considering PAS price.

The OWSA results demonstrated the model was most sensitive to health state costs for the full-time ventilation health state and early ambulatory; the caregiver disutility applied to behavioural issues; the duration of behavioural issues; HRs to the late ambulatory health state; and the average weight for a 4-year-old boy taking vamorolone, when considering the vamorolone PAS price.

Figure 30: Tornado plot of DSA results (incremental costs) for vamorolone vs SoC (list price)

Abbreviations: BOI, burden of illness study; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme; SoC, standard of care

Table 85: DSA results (incremental costs) for vamorolone vs SoC (list price)

Parameter name	Lower incremental costs	Upper incremental costs
Direct costs by health state (BOI) - SoC: 8 - full-time ventilation	[redacted]	[redacted]
Direct costs by health state (BOI) - vamorolone: 8 – full-time ventilation	[redacted]	[redacted]
Behavioural issues: Disutilities	[redacted]	[redacted]
Behavioural issues (caregiver): Duration of event (days)	[redacted]	[redacted]
Vamorolone hazard ratio: To state 2 - Late ambulatory	[redacted]	[redacted]
SoC hazard ratio: To state 2 - Late ambulatory	[redacted]	[redacted]
SoC behavioural issues incidence per cycle: 8b – full-time ventilation	[redacted]	[redacted]
Direct costs by health state (BOI) - vamorolone: 1 - early ambulatory	[redacted]	[redacted]
Direct costs by health state (BOI) - SoC: 1 - early ambulatory	[redacted]	[redacted]

Abbreviations: BOI, burden of illness study; OWSA, one-way sensitivity analysis; PAS, patient access scheme; SoC, standard of care

B.3.11.3. Scenario analysis

Extensive scenario analyses have been conducted in the CEM. The list of scenarios explored is shown in Table 86. Results when considering the vamorolone proposed PAS are provided in Table 87 and indicate that for the majority of scenarios vamorolone remains cost-effective. Results when considering the list price of vamorolone are presented in Table.

Table 86: Scenarios explored in the cost-effectiveness analysis

#	Category	Base case	Scenario	
		Value	Value	Rationale
0	Base case			
1, 2	Time horizon	Lifetime (50 years)	(1) 40 years (2) 60 years	Boys with DMD have a median life expectancy of 29.9 years (range 21.0-36.2)[20] with ventilatory support, a 50yr time horizon is adequate for capturing the all-important difference in costs and outcomes between treatments, in line with the NICE reference case. Time horizons +-10 years were explored to capture the impact of the minority of boys outside the expected mortality age range.
3	Annual discount rate for costs and QALYs	3.5%	1.5%	As per NICE guidelines.[95]
4, 5	Vamorolone down-titration	As per NPP data	(4) All down titrate to 4.0 mg/kg/day (5) 50% down titrate to 4.0 mg/kg/day	(4) Clinical validation proposed that given 4.0 mg/kg/day shows comparable efficacy to 6.0 mg/kg/day, they would recommend all down titrate to 4.0 mg/kg/day. (5) A 50% down-titration rate was explored as an alternative to capture the uncertainty in this parameter.
6, 7	SoC down-titration efficacy	40% of full efficacy	(6) 60% of full efficacy (7) 20% of full efficacy	(6) Clinical validation anticipated non-therapeutic doses of steroids to have around 60% of the efficacy of full recommended dosing. (7) Guglieri et al. (FOR-DMD) presented HR for the relative efficacy for intermittent dosing for reaching disease progression milestones which indicated intermittent dosing had worse efficacy than no treatment, when naively compared to McDonald et al. results. Assuming worse efficacy for suboptimal dosing compared to no treatment is counter-intuitive, therefore a midpoint of 20% is tested.[64,76]
8	AESI grades	Moderate to severe AESIs considered	AESIs of all grades considered	(8) There were limited moderate to severe adverse events recorded in the vamorolone arm therefore the adverse event data for all grades was explored as a scenario.
9, 10	Starting model cohort	4.1 years and 100% in early ambulatory	(9) 5.41 years (10) 5.41 years and 50% early ambulatory	(9) The average age in the pivotal trial, VISION-DMD was 5.41 years old.[4,92] (10) The average age in the pivotal trial, VISION-DMD was 5.41 years old. As the mean age of UK diagnosis is 4.1 years, in a patient cohort of mean age 5.41 years some patients may have progressed to the late ambulatory health state. In this scenario, 50% were assumed to be in the late ambulatory stage.

#	Category	Base case	Scenario	
		Value	Value	Rationale
11	Carer QoL impact	Included	Excluded	(11) To capture the impact of DMD solely on patients.
12	Behavioural issues duration of AE	6 months	1 year	(12) Clinical validation noted behavioural issues usual occur for 6 months at a minimum but often can be ongoing long-term issues. A year scenario was explored to capture this.
13	Health state utilities (patient)	BOI	Landfeldt et al.	(13) Health state utilities were available from Landfeldt et al.; this scenario is explored to test uncertainty around health state utility values.[89]
14	Health state costs (patient and societal)	BOI	Landfeldt et al.	(14) Health state costs were available from Landfeldt et al.; this scenario is explored to test uncertainty around health state costs.[89]
15, 16	Vamorolone stopping rule	At starting night-time ventilation	(15) At loss of HTMF (16) At starting full-time ventilation	It is acknowledged that the stopping rule for vamorolone is currently uncertain, therefore different scenarios explored for an earlier stopping rule (15) at loss of HTMF and a later stopping rule (16) at start of full-time ventilation. Clinical advice received indicates that all scenarios are of potential interest.

Abbreviations: AE – Adverse event; AESI – Adverse event of special interest; BOI – Burden of illness; DMD – Duchenne muscular dystrophy; HR – Hazard ratio; HTMF – Hand-to-mouth function; Kg – Kilogram; Mg – Milligram; NICE – National Institute for Health and Care Excellence; NPP – Named patient programme; QALY – Quality-adjusted life year; QoL – Quality of life; SoC – Standard of care; UK – United Kingdom; Yr – Year.

Table 87: Summary of scenario analyses results for vamorolone vs SoC – PAS price

#	Scenario	Deterministic ICER	Probabilistic ICER
	Base case	[redacted]	[redacted]
1	Time horizon – 40 years	[redacted]	[redacted]
2	Time horizon – 60 years		
3	Annual discount rate for costs and QALYs – 1.5%		
4	Vamorolone down-titration - All down titrate to 4.0 mg/kg/day		
5	Vamorolone down-titration - 50% down titrate to 4.0 mg/kg/day	[redacted]	[redacted]
6	SoC down-titration efficacy - 60% of full efficacy	[redacted]	[redacted]
7	SoC down-titration efficacy - 20% of full efficacy	[redacted]	[redacted]
8	AESI all grades		
9	Starting model cohort 5.41 years	[redacted]	[redacted]
10	Starting model cohort 5.41 years and 50% early ambulatory	[redacted]	[redacted]
11	Exclude carer QoL impact		
12	Behavioural issues duration of AE – 1 year	[redacted]	[redacted]
13	Health state utilities (patient) – Landfeldt et al.	[redacted]	[redacted]
14	Health state costs (patient and societal) – Landfeldt et al	[redacted]	[redacted]
15	Vamorolone stopping rule at loss of HTMF	[redacted]	[redacted]
16	Vamorolone stopping rule at starting full-time ventilation	[redacted]	[redacted]

Abbreviations: AESI – Adverse event of special interest; BOI – Burden of illness; HTMF – Hand-to-mouth function; Kg – Kilogram; Mg – Milligram; QALY – Quality-adjusted life year; QoL – Quality of life; SoC – Standard of care.

Table 88: Summary of scenario analyses results for vamorolone vs SoC – list price

#	Scenario	Deterministic ICER	Probabilistic ICER
	Base case	[redacted]	[redacted]
1	Time horizon – 40 years	[redacted]	[redacted]
2	Time horizon – 60 years	[redacted]	[redacted]
3	Annual discount rate for costs and QALYs – 1.5%	[redacted]	[redacted]
4	Vamorolone down-titration - All down titrate to 4.0 mg/kg/day	[redacted]	[redacted]
5	Vamorolone down-titration - 50% down titrate to 4.0 mg/kg/day	[redacted]	[redacted]
6	SoC down-titration efficacy - 60% of full efficacy	[redacted]	[redacted]
7	SoC down-titration efficacy - 20% of full efficacy	[redacted]	[redacted]
8	AESI all grades	[redacted]	[redacted]
9	Starting model cohort 5.41 years	[redacted]	[redacted]
10	Starting model cohort 5.41 years and 50% early ambulatory	[redacted]	[redacted]
11	Exclude carer QoL impact	[redacted]	[redacted]
12	Behavioural issues duration of AE – 1 year	[redacted]	[redacted]
13	Health state utilities (patient) – Landfeldt et al.	[redacted]	[redacted]
14	Health state costs (patient and societal) – Landfeldt et al	[redacted]	[redacted]
15	Vamorolone stopping rule at loss of HTMF	[redacted]	[redacted]
16	Vamorolone stopping rule at starting full-time ventilation	[redacted]	[redacted]

AE – Adverse event; AESI – Adverse event of special interest; HTMF – Hand-to-mouth function; ICER – Incremental cost-effectiveness ratio; QALY- Quality-adjusted life year; QoL – Quality of life; SoC – Standard of Care

B.3.12. Subgroup analysis

Subgroup analysis was not performed as part of this submission.

B.3.13. Benefits not captured in the QALY calculation

Societal costs are key components in evaluating the cost-effectiveness of treatments in DMD given the substantial burden faced by patients and carers alike, as discussed in Section B.1.3. Health condition and position of the technology in the treatment pathway. Once ambulation is lost and respiratory decline begins, carer burden and time off work increases, emphasising the wider importance of slowing disease progression.[56] Caring for DMD patients is time-consuming and has a severe negative impact in several aspects of daily living including patients and parents' productivity. The economic analysis presented in this submission according to NHS & PSS perspective may miss key aspects of the disease which affects patients and their carers' lives.

B.3.14. Validation

Validation of modelling approach

The model presented in this submission is adapted from the original Project HERCULES model. The structure of the model had already been designed through extensive consultation with patients, caregivers, and clinicians as part of original model development to ensure the model provides a comprehensive picture of the progression of DMD. Throughout the development process, buy-in was sought from manufacturers, HTA experts and health economists to identify characteristics of a therapy, decision problem and audience that would necessitate flexibility within the core model.

Validation of cost-effectiveness inputs and assumptions

Amendments to the original Project HERCULES model used specifically in this analysis were ratified through clinician input to ensure external and clinical validity of both the inputs and assumptions used within the model. Elements of the analysis clinically validated were:

- Use and application of the NHM
- Comparative efficacy of vamorolone, optimal dosed steroids, suboptimal-dosed steroids, and no treatment
- Fracture rates and severity
- Scoliosis and spinal surgery approach
- Vamorolone and corticosteroid dosing
- Resource use associated with adverse events
- Duration of behavioural issues

Validation of cost-effectiveness analysis results

When compared to model outcomes reported in the literature, the QALYs derived in the SoC treatment arm (glucocorticoids) aligned closely with the QALYs reported for glucocorticoids in Landfeldt et al. and Agboola et al.[89,141] Agboola et al. presented 6.88 QALYs for prednisone, and Landfeldt et al. reported 6.93 to 8.13 QALYs across 3 different models which is comparable to the total QALYs reported for SoC and vamorolone within the base case analysis presented in this submission (5.57 and 7.19, respectively). The clinical results of the analysis are therefore in line with available comparable analyses.

B.3.15. Interpretation and conclusions of economic evidence

Over a 50-year time horizon, patients receiving vamorolone accrued 7.19 QALYs at a cost of [redacted], while patients receiving SoC accrued 5.57 QALYs at a cost of [redacted]. The resulting base case ICER was [redacted] per severity-modified QALY meaning vamorolone can be considered [redacted] at a WTP threshold of £30,000 per QALY. When not including carer disutilities, patients receiving vamorolone accrued 8.00 QALYs, while patients receiving SoC accrued 6.88 QALYs.

Probabilistic results were similar to the deterministic results demonstrating the robustness of the base case results. OWSA found that results were most sensitive to the direct health state costs for full-time ventilation in both treatment arms and the early ambulatory health state cost for vamorolone. Extensive scenario analysis found that the majority of scenarios produced comparable ICERs to the base case.

The clinical of the model are comparable to results seen in the literature, further reinforcing the credibility of the analysis. In this context, vamorolone can therefore be considered a [redacted] use of NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Vamorolone for treating inflammation associated with Duchenne muscular dystrophy [ID4024]

Summary of Information for Patients (SIP)

October 2023

File name	Version	Contains confidential information	Date
[ID4024]_vamorolone_SIP	**1.0**	**Yes**	**4 October 2023**

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

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Vamorolone (Agamree®).

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Final scope issued by the National Institute for Health and Care Excellence (NICE) Vamorolone for treating Duchenne muscular dystrophy (DMD). **Decision problem addressed in the Company Submission** The purpose of this submission is to achieve reimbursement (funding on the National Health Service) for vamorolone in patients aged [redacted] This population is in line with the anticipated license for vamorolone.

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.

Marketing authorisation for vamorolone is pending.

European Medicines Agency (EMA)

Within the European Union, marketing authorisation is currently under review by the EMA, with an expected approval in [redacted]

The Medicines and Healthcare products Regulatory Agency (MHRA)

Within the United Kingdom (UK), a marketing authorisation submission to the MHRA will be made on receipt of a positive Committee for Medicinal Products for Human Use (CHMP) opinion via the European Commission Decision Reliance Procedure.

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:

Santhera Pharmaceuticals is a partner of the Duchenne UK-led project HERCULES. Santhera is a sponsor of patient and parent group meetings organised by Duchenne UK and by Action Duchenne.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

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.

DMD is one of the most common and severe forms of muscular dystrophy

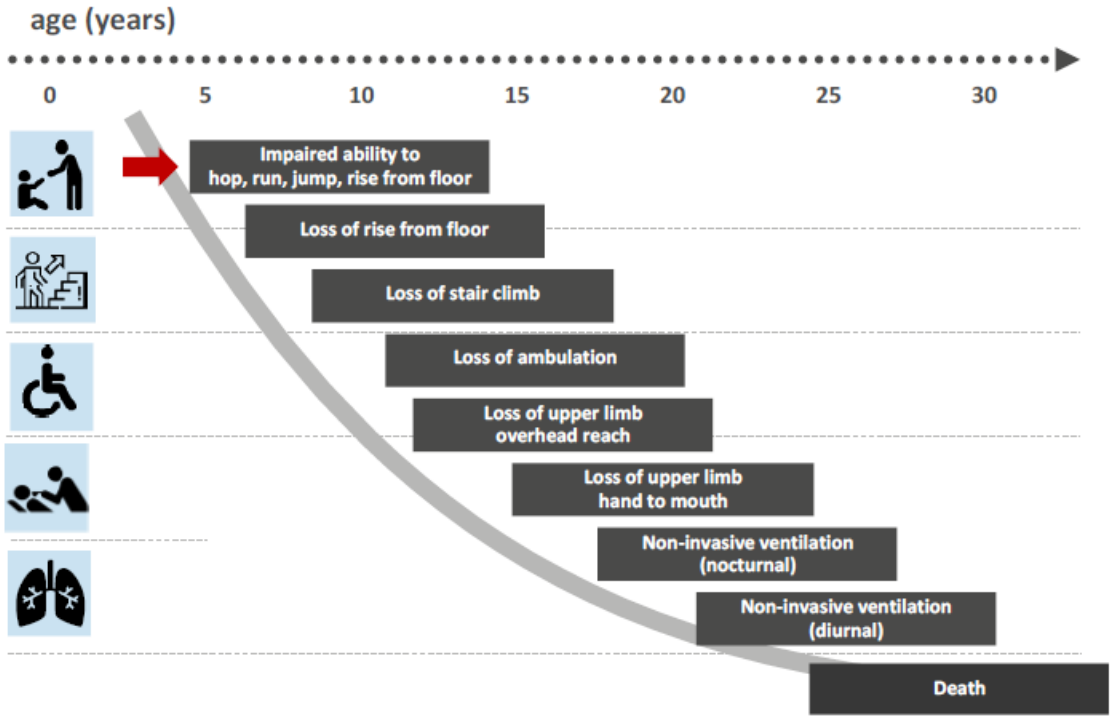
DMD is a genetic disorder characterised by debilitating muscle degeneration and weakness leading to progressive and severe long-term disability.[1,2] The average age at diagnosis in the UK is 4.1 years old.[3] Early signs of DMD include:[4]

- Large calf muscles (known as pseudohypertrophy),
- Delay in the ability to sit and stand independently,

- Use of a Gower's movement to stand (walking hands up the legs to rise),
- Unusual gait when walking.

From the start of symptom presentation, DMD results in a rapid progression of muscle weakness and degeneration, as shown in Figure 1. Major stages in the disease are the loss of ambulation, the loss of self-feeding and the irreversible initiation of assisted ventilation.[1,5] Mean life expectancy for patients with DMD is 30 years with causes of death mostly due to respiratory and/or cardiac failure.[6–8]

Figure 1: Typical muscle degeneration seen in patients with DMD



Abbreviations: DMD – Duchenne muscular dystrophy
Source: Data on file.

DMD is one of the most common forms of childhood muscular dystrophy, with a worldwide birth incidence of around 1 in 5,050 boys [8]

In the UK, approximately 100 boys are born each year with DMD, and it is thought that around 2,500 people will be living with the condition in the UK at any one time.[9] As this mutation occurs on the X chromosome, there is an almost exclusive prevalence of DMD in males since they only have one copy of the dystrophin gene. Female cases of DMD are extremely rare, around 1 case per 50 million births,[10] due to the existence of the additional X chromosome, which generally allows for sufficient dystrophin production.

DMD is associated with a significant burden to both patients and caregivers

DMD is associated with significant disease-related burden for patients, families and caregivers in terms of physical, health, logistical, emotional and psychological-demands as well as financial burden.[11–21]

Given that symptoms can start presenting in children as young as two years old, patients with DMD live their whole life with gradually increasing physical impairment and dependency on other people.[22] In the early stages, these symptoms include difficulty climbing stairs, walking and standing, resulting in frequent falls and considerably greater risks of fractures, causing greater physical burden and consequently demanding greater carer supervision. Physical impairment is particularly substantial in non-ambulant patients due to a general lack of strength and fatigue. Muscle weakness can hamper chewing and swallowing whilst cognitive impairment can lead to speech problems such as late onset of speaking, problems with word finding and difficulty in fluent language production.[21] Patients can tire more easily due to the increased effort required to engage in daily activities, limiting their ability to participate freely with their peers.[19,21] This can result in psychological issues due to patients' increasing awareness of their disease and the impact this has on emotional well-being, leading to depression and anxiety. Some children also present with learning and behavioural difficulties, which have additional detrimental effects surrounding their social and academic capacities.

The burden, and therefore the impact on the carers, is significant, even when patients have electrical wheelchairs, cough assist equipment, transfer lifts, hand-function assist devices and ventilators. The care of patients becomes 24/7 once patients are on full-time ventilation. As such, the need for round the clock medical care has a significant impact on the patient's ability to work and need for unpaid care over their lifetime. In addition to informal care, there is a need for care provided by paid professionals, the cost of which would be absorbed by the National Health Service (NHS) and Personal Social Services (PSS). Parents experience poor and frequently interrupted sleep due to needs such as changing bed position or checking ventilation. Siblings are often required to take care of the patient, which can lead to the onset of practical and psychological difficulties.[23]

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?

In diagnosing DMD, a doctor usually begins by taking patient and family history and performing a physical examination. Doctors may find pseudohypertrophy, lumbar spine deviation, gait abnormalities, and several grades of diminished muscle reflexes.[24]

Much can be learned from these observations, including the pattern of weakness. A patient's history and physical examination go a long way toward making a diagnosis, even before any of the following diagnostic tests are carried out:[24]

- Creatine kinase blood test,
- Genetic blood test,
- Muscle biopsy.

No additional diagnostic tests beyond the usual practice are required with vamorolone.

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.

There is no curative treatment for DMD and therefore, current treatment goals are aimed at delaying disease progression for as long as possible, and to anticipate and manage the associated complications, such as joint contractures, scoliosis, bone fractures, cardiomyopathy, respiratory insufficiency and treatment-related adverse events.[25] A multidisciplinary approach is required to effectively manage patients. This includes neuromuscular management, rehabilitation interventions (such as physiotherapy, occupational therapy and speech language therapy), orthopaedic and surgical management, gastrointestinal and nutritional management, psychosocial, respiratory and cardiac management.[2,5]

Ataluren (Translarna) is a recently developed treatment; it is used to treat patients aged 2 years and older with DMD who are able to walk. In Europe, this is the sole product with a marketing authorisation for DMD.[26] However, it is only indicated in a small group of

patients whose disease is caused by a specific genetic defect (called a 'nonsense mutation') in the dystrophin gene and treatment with ataluren must be discontinued as soon as the patient is no longer ambulant.[27]

Despite not being indicated for the treatment of DMD in the UK, glucocorticoids, including long-term prednisone or deflazacort dosing, are the current standard of care for DMD, as per the International DMD Care Considerations guidelines.[28] They are typically introduced between four to seven years old when muscle function decline becomes more pronounced. Glucocorticoids remain the mainstay of treatment, and treatment typically continues even after loss of ambulation.[2] Although glucocorticoids have demonstrated significant benefits, they are associated with a number of severe side effects.[29]

The side effects of glucocorticoids include osteoporosis, reduced bone strength and increased risk of fractures, resulting from the potent osteotoxicity of glucocorticoid therapy combined with progressive myopathy.[16,30] This has an evident impact on patient mobility and independence, requiring additional reliance on others during recovery. Stunted growth is a common side effect of glucocorticoid treatment. In combination, these adverse bone and growth outcomes result in a shorter stature and negatively impact patient self-esteem and well-being.[31] Glucocorticoids exacerbate the complex natural history of weight gain and weight maintenance in males with DMD, especially in non-ambulatory patients.[30] Such weight gain is associated with obstructive sleep apnoea. Further side effects of glucocorticoids reported by DMD patients are severe mood swings and psychological effects, as well as Cushingoid features, adrenal suppression, insulin resistance and diabetes, cataracts and growth and development impediments.[30,32,33] In non-randomised studies, these side effects have been identified as clinically meaningful adverse events associated with the long-term use of glucocorticoids.[16,30–33] The severe side effects of glucocorticoids have been reported to impact therapeutic dosing and discourages many patients and their carers to initiate or continue with treatment.[34] Research suggests that side effects are responsible for approximately 65% of corticosteroid discontinuation, meaning these patients are not receiving the full remit of benefits available with current treatment.[35]

Vamorolone is anticipated to be offered to all patients with DMD aged two years and older.

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.

Project HERCULES

Project HERCULES is a unique initiative led by Duchenne UK to develop tools and evidence to support Health technology assessment (HTA) and reimbursement decisions for new treatments for DMD; numerous stakeholders were brought together, including patient organisations. One of the key outputs from this initiative was the development of a cost-effectiveness model (CEM).

The project HERCULES CEM was deemed to have the most relevant structure to model vamorolone for this appraisal; (see 3j for more information).

Health-state costs comprising of medical and non-medical costs in the economic model were sourced from the burden of illness (BOI) study that was conducted as part of project HERCULES. This study is a bottom-up prevalence-based BOI study based across the UK. The study combined real-world data and relevant sets of measurements to provide robust evidence for the identification of unmet needs and estimate the total annualised cost of the disease.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

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.

Overview of vamorolone

The summary of product characteristics (SmPC) and patient information leaflet for vamorolone will be published in due course.

Published information on vamorolone is available on the Santhera website: https://www.santhera.com/health-care-professionals/vamorolone

The mechanism of action of vamorolone is through several pathways

Vamorolone binds to the [redacted]

and is a [redacted]

Vamorolone has a different molecular backbone than classical glucocorticoids. In a clinical study, patients on prednisone in the first 24 weeks showed reduced growth. When patients switched from prednisone to vamorolone, this growth stunting was reversed, and normal growth was seen.[36] In the same study, vamorolone also had an improved safety profile relative to prednisone with respect to behaviour. In addition, bone biomarkers were reduced with prednisone and were not reduced with vamorolone.[36]

In clinical trials, vamorolone has shown a reduced rate of bone fractures, loss of Cushingoid features in patients, loss of insulin resistance, and small proportions of patients have shown a gain in weight over 18 months of treatment.[36–39]

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.

Vamorolone is not intended to be used in combination with any other medicines.

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?

Vamorolone is for oral use and can be taken with or without a meal. The oral suspension requires redispersing by shaking the bottle for about 30 seconds before dosing. Vamorolone is administered orally with a syringe which should be dispensed directly into the mouth.[40]

2 to below 4 years of age

The recommended starting dose of vamorolone is [redacted] After [redacted] months, the dose should be increased to [redacted] Daily dose may be [redacted] to [redacted] based on individual tolerability.

4 years and older

The recommended dose of vamorolone is [redacted] in patients weighing less than [redacted] In patients weighing [redacted] the recommended dose of vamorolone is [redacted] Daily dose may be reduced to [redacted] or [redacted] based on individual tolerability.

[redacted]

Treatment with vamorolone should only be initiated by specialist physicians with experience in DMD.[40] Once treatment is initiated, vamorolone can be administered at home. Administration is not expected to be significantly different to existing treatments; Prednisone is available in tablet and liquid form, whilst deflazacort is available in tablet form.[9]

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.

The clinical effectiveness of vamorolone in the treatment of DMD was assessed in an extensive clinical trial programme (Table 1). The pivotal trial to assess clinical effectiveness is the VISION-DMD study (VBP15-004). In addition to the pivotal study, vamorolone was assessed in three Phase II studies (VBP15-002/003/LTE).

Table 1: Overview of the vamorolone clinical trial program

Title	Location	Population	Intervention(s)	Comparator(s)	Key inclusion criteria	Completion dates	References
VISION-DMD (VBP15-004) NCT03439670	33 study locations.	Ambulatory boys aged 4 to <7 years with DMD who were corticosteroid-naïve at study entry.	**Period 1:** Vamorolone 2.0 mg/kg/day, Vamorolone 6.0 mg/kg/day. **Period 2:** Vamorolone 2.0 mg/kg/day, Vamorolone 6.0 mg/kg/day.	**Period 1:** Prednisone 0.75 mg/kg/day, Placebo **Period 2:** **None** All patients who were previously treated with either prednisone or placebo were treated with vamorolone 2.0 or 6.0 mg/kg/day	Males aged 4 to <7 years, with a DMD gene loss-of-function variation or lack of muscle dystrophin.	**Primary completion date:** February 23, 2021. **Study completion date:** August 19, 2021.	Guglieri et al.[36]

VBP15-002; NCT02760264	12 study locations.	Boys aged 4 to <7 years with DMD.	Vamorolone 0.25 mg/kg/day, Vamorolone 0.75 mg/kg/day, Vamorolone 2.0 mg/kg/day, Vamorolone 6.0 mg/kg/day.	N/A	Male subjects, 4 - <7 years of age at study entry, diagnosed with DMD by confirmed dystrophin deficiency.	**Primary completion date:** May 1, 2018. **Study completion date:** May 1, 2018.	Conklin et al.[38]
VBP15-003; NCT02760277	12 study locations.	Boys with DMD who had completed Study VBP15-002.	Vamorolone 0.25 mg/kg/day, Vamorolone 0.75 mg/kg/day, Vamorolone 2.0 mg/kg/day, Vamorolone 6.0 mg/kg/day.	N/A	Males with confirmed DMD who had completed Study VBP15-002.	**Primary completion date:** April 26, 2018. **Study completion date:** April 26, 2018.	Hoffman et al.[41]
VBP15-LTE; NCT03038399	12 study locations.	Boys with DMD who had completed VBP15-003.	Vamorolone 0.25 mg/kg/day, Vamorolone 0.75 mg/kg/day, Vamorolone 2.0 mg/kg/day, Vamorolone 6.0 mg/kg/day.	N/A	Males with confirmed DMD who had completed Study VBP15-003.	**Primary completion date:** April 30, 2020. **Study completion date:** April 30, 2020.	Mah et al.[42]

Abbreviations: DMD - Duchenne muscular dystrophy; kg – kilogram; mg – milligram.

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.

The efficacy of vamorolone was studied and established in a phase IIb randomised controlled trial (VISION-DMD). The doses studied in VISION-DMD were established in two Phase IIa studies conducted back-to-back in 48 boys with DMD aged 4 to <7 years (VBP15-002 and VBP15-003). The long-term effect of vamorolone has been studied in the open-label extension study (VBP15-LTE).

VISION-DMD

VISION-DMD investigated the safety and efficacy of vamorolone 2.0 and 6.0 mg/kg/day versus prednisone 0.75 mg/kg/day and placebo. The objective of VISION-DMD was to assess the longer-term efficacy of vamorolone and establish whether benefits seen after 24 weeks could be maintained to 48 weeks.

Time to stand from supine (TTSTAND) velocity was significantly improved with vamorolone 6.0 mg/kg/day compared with placebo.[36] The improvement seen with vamorolone is predictive of a delay of 2-3 years until loss of ambulation.[43] The clinically meaningful improvement seen with vamorolone 6.0 mg/kg/day was maintained at Week 48.

In addition, changes in a range of bone biomarkers were improved in both vamorolone groups whilst significant reductions were seen after treatment with prednisone.[36]

VBP15-002 & VBP15-003

These studies investigated the efficacy, safety, and tolerability of vamorolone at doses of 0.25, 0.75, 2.0 and 6.0 mg/kg/day. The key objective of the studies was to assess if an increase in dose of vamorolone led to an equivalent improvement in gross motor strength and endurance. The studies also aimed to assess the safety of vamorolone compared to glucocorticoids.

In VBP15-002, vamorolone was safe and well-tolerated up to the highest dose tested of 6.0 mg/kg/day.[38]

In VBP15-003, vamorolone was safe and well-tolerated at all doses with no adverse events leading to reduction of drug dosing or withdrawal from the trial.[41]

VBP15-LTE

Following completion of VBP15-003, patients were eligible for a 2-year long-term extension treatment period. In longitudinal comparison of mean TTSTAND, time to run/walk 10 metres (TTRW), time to climb four stairs (TTCLIMB) velocity and from baseline to end of follow-up, the LTE group and Duchenne Natural History Study group were not significantly different.[42]

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.

In the VISION-DMD trial, quality of life (QoL) was measured through the Paediatric Outcomes Data Collection Instrument (PODCI), Treatment Satisfaction Questionnaire (TSQM) and the Psychosocial Adjustment and Role Skills Scale III (PARS III) questionnaire.

- **PODCI** consists of 83-86 questions and five subscale scores with scores ranging from 0-100, where lower scores indicate lower health-related quality of life (HRQL),
- **TSQM** measures treatment satisfaction and consists of four subscales: global satisfaction, effectiveness, side effects, and convenience,
- **PARS III** questionnaire consists of 28 questions in six areas: peer relations, dependency, hostility, productivity, anxiety-depression, and withdrawal.

Results for both the PODCI and TSQM showed no significant differences between patients who received vamorolone and patients who received placebo in the VISION-DMD clinical trial.[36] Importantly, vamorolone showed improvement compared to prednisone; this indicates that DMD patients could have a better QoL with vamorolone in comparison to current standard of care. Additionally, The PARS III questionnaire suggested that vamorolone 2.0 mg/kg/day showed better adjustment for anxiety and depression compared with prednisone.

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.

Like all medicines, vamorolone can cause side effects. The following side effects are listed in the SmPC:

Very common (may affect more than 1 in 10 people)

[redacted]

Common (may affect up to 1 in 10 people)

[redacted]

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed above. You can also report side effects directly via the national reporting system (santhera@EU.propharmagroup.com). By reporting side effects, you can help provide more information on the safety of this medicine.

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

Vamorolone is an effective treatment and had an improved safety profile relative to prednisone with respect to behaviour-related side effects, growth stunting, and deleterious changes in bone biomarkers.

As detailed in 3k), there is no curative treatment for DMD, and current standard of care is unlicensed. Vamorolone is safe and well-tolerated, showing a reduction in adverse events typically seen in DMD patients treated with long-term glucocorticoids. As detailed in 2c),

glucocorticoids are associated with a number of side effects, some of which can be severe. The clinically significant side effects of glucocorticoids have been reported to impact effective dosing and discourages many patients and their carers to initiate or continue with treatment.[34] Thus, an improved safety profile will encourage patients to remain on-treatment and consequently receive the full beneficial effects of vamorolone.

As detailed in 3e), the clinical effectiveness of vamorolone has been examined in a robust clinical trial program (VBP15-002/003/LTE and the pivotal study, VISION-DMD); results have shown that vamorolone provides equal efficacy to glucocorticoids and as detailed in 3f), it improves QoL in comparison to current standard of care.

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

Please refer to 3g) for information relating to the side effects of vamorolone.

Vamorolone is administered orally using a syringe. This may be problematic for some patients, particularly children, in terms of taste and palatability. One of the key disadvantages of using an oral syringe is the potential inability to measure and administer a precise dose of medication. Errors in measuring the medication can result in over or under-dosing, which can impact the effectiveness and safety of the treatment.

To mitigate the challenges associated with the use of an oral syringe for administering vamorolone, caregivers should provide assistance, particularly to measure the prescribed dose (as detailed in the SmPC).

Additionally, patients with advanced DMD may require tube feeding. The administration of vamorolone through the gastrointestinal (GI) or percutaneous endoscopic gastrostomy (PEG) tube is currently undergoing investigation. Consequently, there is currently no available data regarding this method of administration.

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.

For a treatment to be reimbursed by the NHS, the manufacturer must provide an economic model (also called a cost-effectiveness or cost-utility model) to demonstrate that the treatment will provide value for money in the NHS. An overview of the economic model for vamorolone is provided below.

How the model reflects the condition

The economic model estimates the costs and benefits for patients receiving vamorolone. Standard of care (SoC) is the primary comparator in the model, consisting of the glucocorticoids, prednisone and deflazacort.

The model attempts to reflect the full disease pathway of DMD, comprising ambulatory and non-ambulatory health states. Patients transition through each health-state sequentially. Each of these health states are associated with specific costs and levels of quality of life (QoL,referred to as "utility").

Modelling how much a treatment extends life and improves QoL

Patients who receive vamorolone have a lower risk of experiencing severe side effects compared to SoC (see 2c) for more information). The improved safety profile with vamorolone will encourage patients to remain on-treatment and consequently receive the full beneficial therapeutic

effects of vamorolone. DMD substantially reduces QoL; as detailed in 3f), patients who receive vamorolone are less likely to experience these QoL reductions, from reduced side effects versus SoC and better tolerability, meaning patients can remain on therapeutic dosing for longer.

In order to assess the impact of vamorolone in comparison to SoC in terms of quantity and QoL, Quality-adjusted life year (QALY) is used as a summary measure in the economic model.

Modelling how the costs of DMD differ with the new treatment

Costs considered in the model include drug acquisition and administration costs, in addition to medical resource use costs, including general resource use (such as regular specialist appointments) and costs associated with side effects (for instance emergency hospital visits). Cost data are based on published literature and UK national databases.

Uncertainty

The model tested many alternative assumptions and data sources via extensive sensitivity analyses.

Cost-effectiveness results

Cost-effectiveness results for vamorolone compared to SoC have been presented in the Company Submission. The body deciding whether to recommend new treatments for reimbursement within the NHS is called NICE. A treatment is typically considered value for money for the NHS if it can provide patients with one year of life at perfect health for a cost between £20,000 and £30,000.

The results of the CEM for vamorolone estimate that vamorolone is likely to be considered cost-effective. This means that if NICE agree with the assumptions and estimations included in the Santhera economic model, then vamorolone should represent value for money for the NHS when used in the target population.

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)
Vamorolone is an innovative medicine which has the potential to address a substantial unmet need for patients There is no curative treatment for DMD and current SoC (i.e., glucocorticoids) is unlicensed and associated with a number of severe side effects. As such, there is a significant unmet need for an effective, licensed treatment that has equal efficacy to existing therapies, but that minimises the risks of damaging side effects associated with current SoC, encouraging greater uptake and continuation of treatment. **Promising Innovative Medicine (PIM)** A PIM designation is an early indication that a medicinal product is a promising candidate for the Early Access to Medicines Scheme (EAMS); vamorolone has received such designation.

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. 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 More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Santhera do not expect assessment of this technology to raise any equality issues.

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.
Please refer to Table 1 for publications on the safety, efficacy and effectiveness of vamorolone.

Further information on NICE and the role of patients**:**

- 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 [44,45]

6MWT – Six-minute walk test. A test to measure how far a patient can walk for 6 minutes, commonly used as a measure in DMD clinical trials.

Adverse event – When a patient experiences an undesirable side effect associated with the use of a medical product. The event is considered serious if it results in death, hospitalisation, or prolongation of existing hospitalisation, persistent or significant disability/incapacity or a congenital anomaly or birth defect.

Biomarker – a biomarker is anything found in the body that can be used to measure the state of the body. They can be found in saliva, urine, or blood. In clinical trials, they are used to measure whether a drug is having any effect on the body.

Biopsy – Removing a sample of tissue (such as muscle) from the body so the tissue can be examined. This may be to understand more about the state of the muscle. Biopsies are

used in clinical trials to examine the muscle and look at whether treatments may be having an effect.

BOI – Burden of illness. Designed to estimate the economic impact of a particular disease on a particular society in monetary terms.

Cardiac – Anything to do with the heart.

Cardiomyopathy – Cardiomyopathy is a disease of the heart muscle that makes it harder for your heart to pump blood to the rest of your body. Cardiomyopathy can lead to heart failure.

Cell – The smallest structural units of living matter that all living things are composed of.

Chromosome – Long strings of genetic material made up of DNA and accessory proteins. The DNA contains approximately 30,000 to 100,000 genes that make up the human genome. Chromosomes come in pairs, and a normal human cell contains 46 chromosomes, 22 pairs of autosomes and two sex chromosomes.

Clinical trial stages – Phase 1: Determining which dose is safe, how often if should be given and the best form of treatment. Few participants. Phase 2: Assessing the effectiveness of the treatment, its side effects and tolerance levels. More participants. Phase 3: Determining whether the new treatment works better than an alternative current standard treatment.

Corticosteroid – A type of drug similar to natural hormones produced by the adrenal glands that reduce inflammation and suppress the immune response. The main one used in the UK is called prednisolone (prednisone in the USA and Europe) Deflazacort is also used in some countries.

Dystrophin – A protein found in skeletal muscle, which people with DMD are unable to create. Dystrophin is one of a group of proteins that work together for muscle function, to strengthen muscles and protect them from injury.

HTA - Multidisciplinary research process that collects and summarises information about a health technology.

Inflammation – A part of the body's natural reaction to infection or trauma. It occurs in muscle cells after they have been damaged and is due to a lack of dystrophin. The prevention of inflammation is important in stopping the progression of DMD.

Myopathy – A condition affecting muscle, usually without involvement of the nerves.

Natural history – The usual course or development of a disease or condition, especially in the absence of treatment. A natural history study collects health information in order to understand how the medical condition or disease develops and how to treat it.

Placebo – A substance that has no therapeutic effect. Placebos are used as a control in testing new drugs, to see if the drug being tested is having an effect.

QALY – Quality-adjusted life years. The academic standard for measuring how well all different kinds of medical treatments lengthen and/or improve patients' lives.

Randomised controlled trial – A clinical trial where treatments and placebo are allocated randomly to participants rather than by conscious decisions of clinicians or patients.

Scoliosis – Curvature of the spine.

Tissue – A group of cells that carry out a particular job or function.

TTCLIMB – Time to climb four stairs. The number of seconds taken to walk up four stairs.

TTSTAND – Time to stand from supine. The number of seconds taken to rise from a supine (lying down on your back) position to stood up, without assistance. This is a useful functional test in DMD and is often used as a primary or secondary endpoint in clinical trials.

TTRW – Time to run/walk 10 metres. The number of seconds taken to run or walk 10 metres.

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:

1. Fayssoil A, Abasse S & Silverston K. Cardiac Involvement Classification and Therapeutic Management in Patients with Duchenne Muscular Dystrophy. *J Neuromuscul Dis* 2017. 4: 17–23.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Clarification questions

November 2023

File name	Version	Contains confidential information	Date
[ID4024]_vamorolone_EAG _clarification_questions_[redacted]	Final	Yes	10/11/2023

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

A1. In Table 42 and in Section B.3.4.5 of the CS, the company state that EQ-5D was collected in the VISION-DMD trial, but this was not presented. Please can the company present these data.

This was an error within the submission; no EQ-5D data was collected in the VISION-DMD trial.

A2. Please complete the following tables with results not presented in the CS (Doc B).

Table 1: TTSTAND velocity change from baseline to Week 24: vamorolone 2.0 mg/kg/day versus prednisone (mITT-1 population)

TTSTAND Velocity (rises/sec)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)
Baseline, mean (SD)	[redacted]	0.18 (0.05)
Week 24, mean (SD)	[redacted]	[redacted]
Change from baseline at Week 24, mean (SD)	[redacted]	[redacted]
LSM (SE) change from baseline	[redacted]	0.03 (0.01)
LSM difference (SE) vs prednisone	[redacted]	
95% CI vs prednisone	[redacted]	
p-value vs prednisone	[redacted]	

Note: Change from baseline at Week 24, mean (SD) for vamorolone 2.0 mg/kg/day (n=30) has been updated to reflect the VISION-DMD CSR.[1]
Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT-1 – Modified Intent-to-treat (period 1); SD – Standard deviation; SE – Standard error; Sec – Second; TTSTAND – Time to stand from supine.
Source: VISION-DMD CSR.[1]

Table 2: TTRW velocity change from baseline to Week 24: vamorolone versus prednisone (mITT-1 population)

TTRW velocity (metres/sec)	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=30)	Vamorolone 2.0 mg/kg/day (n=30)
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Week 24, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24, mean (SD)	[redacted]	0.28 (0.28)	0.16 (0.23)
LSM (SE) change from baseline	[redacted]	[redacted]	[redacted]
LSM difference (SE) vs prednisone	NA	[redacted]	[redacted]
95% CI vs prednisone	NA	[redacted]	[redacted]
p-value vs prednisone	NA	[redacted]	[redacted]

Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT-1 – Modified Intent-to-treat (period 1); NA – Not applicable; SD – Standard deviation; SE – Standard error; Sec – Second; TTRW – Time to run/walk 10m.
Source: VISION-DMD CSR.[1]

Table 3: Change from baseline to Week 24 in TTCLIMB velocity: vamorolone vs prednisone (mITT-1 population)

TTCLIMB velocity (tasks/sec)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	[redacted]	0.20 (0.05)	0.21 (0.09)
Week 24, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24, mean (SD)	[redacted]	[redacted]	[redacted]
LSM (SE) change from baseline	[redacted]	0.05 (0.02)	0.06 (0.01)
LSM difference (SE) vs prednisone	NA	[redacted]	[redacted]
95% CI vs prednisone	NA	[redacted]	[redacted]
p-value vs prednisone	NA	[redacted]	[redacted]

Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT-1 – Modified Intent-to-treat (period 1); NA – Not applicable; SD – Standard deviation; SE – Standard error; Sec – Second; TTCLIMB – Time to climb 4 stairs.
Source: VISION-DMD CSR.[1]

Table 4: Change from baseline to Week 24 in NSAA score: vamorolone vs prednisone (mITT-1 population)

NSAA score	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	[redacted]	17.2 (4.66)	18.9 (4.07)
Week 24, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24, mean (SD)	[redacted]	[redacted]	[redacted]
LSM (SE) change from baseline	[redacted]	2.52 (0.63)	2.85 (0.61)
LSM difference (SE) vs prednisone	NA	[redacted]	[redacted]
95% CI vs prednisone	NA	[redacted]	[redacted]
p-value vs prednisone	NA	[redacted]	[redacted]

Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT-1 – Modified Intent-to-treat (period 1); NA – Not applicable; NSAA – North Star Ambulatory Assessment; SD – Standard deviation; SE – Standard error.
Source: VISION-DMD CSR.[1]

Table 5: Knee extension muscle strength: vamorolone vs prednisone (mITT-1 population)

Knee extension muscle strength	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Week 24, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24, mean (SD)	[redacted]	[redacted]	[redacted]

LSM (SE) change from baseline	[redacted]	[redacted]	[redacted]
LSM difference (SE) vs prednisone	NA	[redacted]	[redacted]
95% CI vs prednisone	NA	[redacted]	[redacted]
p-value vs prednisone	NA	[redacted]	[redacted]

Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT-1 – Modified Intent-to-treat (period 1); NA – Not applicable; SD – Standard deviation; SE – Standard error.
Source: VISION-DMD CSR.[1]

Table 6: Elbow flexor muscle strength: vamorolone vs prednisone (mITT-1 population)

Elbow flexor muscle strength	**Prednisone (n=31)**	**Vamorolone 2.0 mg/kg/day (n=30)**	**Vamorolone 6.0 mg/kg/day (n=28)**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Week 24, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24, mean (SD)	[redacted]	[redacted]	[redacted]
LSM (SE) change from baseline	[redacted]	[redacted]	[redacted]
LSM difference (SE) vs prednisone	NA	[redacted]	[redacted]
95% CI vs prednisone	NA	[redacted]	[redacted]
p-value vs prednisone	NA	[redacted]	[redacted]

Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT-1 – Modified Intent-to-treat (period 1); NA – Not applicable; SD – Standard deviation; SE – Standard error.
Source: VISION-DMD CSR.[1]

A3. In Table 2 of the CS, it is stated that vamorolone leads to less frequent cushingoid appearance than prednisone. However, the proportion of participants with cushingoid features was higher in the vamorolone 6.0 mg/kg/day arm than the prednisone arm at 24 weeks in the VISION-DMD trial. Are the results of the double-blind period of the VISION-DMD trial incompatible with the statement on cushingoid appearance in Table 2 of the CS?

The company acknowledges that the proportion of participants with cushingoid features was higher in the vamorolone 6.0 mg/kg/day arm in comparison to the prednisone arm at Week 24 in the VISION-DMD trial (prednisone arm = seven patients vs vamorolone 6.0 mg/kg/day arm = eight patients). However, while eight patients receiving vamorolone 6.0 mg/kg/day reported cushingoid features at Week 24, by Week 48, only one patient reported this adverse event. This indicates there is a lower incidence of developing cushingoid features after the first six months of therapy at this dose.

A4. The population in the decision problem addressed by the company are people with DMD aged two years and older. However, the pivotal trial (VISION-DMD), recruited children with DMD who are aged four to seven years old. The EAG understand the company is currently conducting VBP15-006, a phase II trial in boys aged 2 to <4 Years and 7 to <18 Years with DMD. However, this is an ongoing trial and no preliminary results have been presented in the CS. Please can the company provide a clinical rationale why recommendations can be made in these age groups, prior to seeing efficacy and safety data from the VBP15-006 trial.

Since the company submission, vamorolone has received a positive Committee for Medicinal Products for Human Use (CHMP) opinion for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older. Therefore, patients younger than 4 years of age will not be treated with vamorolone.

Extrapolation of efficacy and safety data from the VISION-DMD study population (patients 4 to <7 years of age)[2–4] to DMD patients ≥7 years and over, including patients in the ambulatory declining and non-ambulatory phase of the disease, is supported by the same pharmacological mechanism of DMD, while the risks appear not different.

Based on the same pathomechanism with inflammation being present across all stages of the disease, extrapolation of efficacy for vamorolone is supported as per the CHMP assessment report.[5] Although data on corticosteroid treatment in boys with DMD are generally limited and scientific knowledge regarding the appropriate treatment duration is still evolving, corticosteroids are recommended in the decline phase and early non-ambulatory phase of the disease. Studies have shown that steroid use after loss of ambulation in DMD was associated with delayed progression of important pulmonary, cardiac and upper extremity functional deficits (McDonald et al, 2023).[6] In addition, it is recommended to continue treatment after loss of ambulation. Considering that the pharmacological mechanism that mediates efficacy of vamorolone in the treatment of DMD is the same as for currently used corticosteroids, extrapolation of these recommendations to vamorolone is justified.[5]

In terms of safety, this has been determined in patients 4 to <7 years of age. As per the CHMP assessment report, for patients beyond 7 years of age, extrapolation of

clinical safety from the reference population studied in the VISION-DMD trial can be supported by the available data from study VBP15-006,[7] extension study VBP15-LTE,[8,9] and patients being followed-up in Expanded Access Programmes.[5]

A5. In table 2 of the CS, it is stated that treatment with glucocorticoids is part of the standard of care for both ambulatory and non-ambulatory patients with DMD. Given this statement, and given the permitted and prohibited medications (Table 9 in Doc B), what proportion of people with DMD under NHS care receive medications in line with that received by the placebo arm in the VISION-DMD trial?

Glucocorticoids, including long-term prednisone or deflazacort dosing, are recommended in the International standards of care guideline for DMD[10], which has been accredited by the National Institute for Health and Care Excellence (NICE). There is no direct data available on the proportion of people with DMD under National Health Service (NHS) care that receive glucocorticoids. However, Joseph et al. 2019 conducted research which aimed to evaluate fracture incidence and linear growth impairment from a national cohort of boys with DMD in the United Kingdom (UK), the NorthStar database.[11] The NorthStar database was established in 2006 to collect data from children with DMD followed in all the major paediatric neuromuscular centres in the UK. Of the 832 participants from 2006-2015 who were included in the aforementioned study, 76.7% were receiving glucocorticoids at baseline and 82.6% at last visit. These figures are anticipated to be reflective of the care provided by the NHS.

The above figures (NorthStar database) will not be in line with those received by the placebo arm in the VISION-DMD trial. This is because standard of care (SoC) is represented by the prednisone arm. The eligibility criteria of the placebo arm required patients to be steroid-naïve at study entry; this ensured placebo patients were limited in their exposure to steroids; only [redacted] of placebo patients received steroids during the initial 24-week period.

A6. The subgroup analysis presented in B.2.7 used the vamorolone versus placebo comparison. Please present the subgroup analysis for the vamorolone versus prednisone comparison.

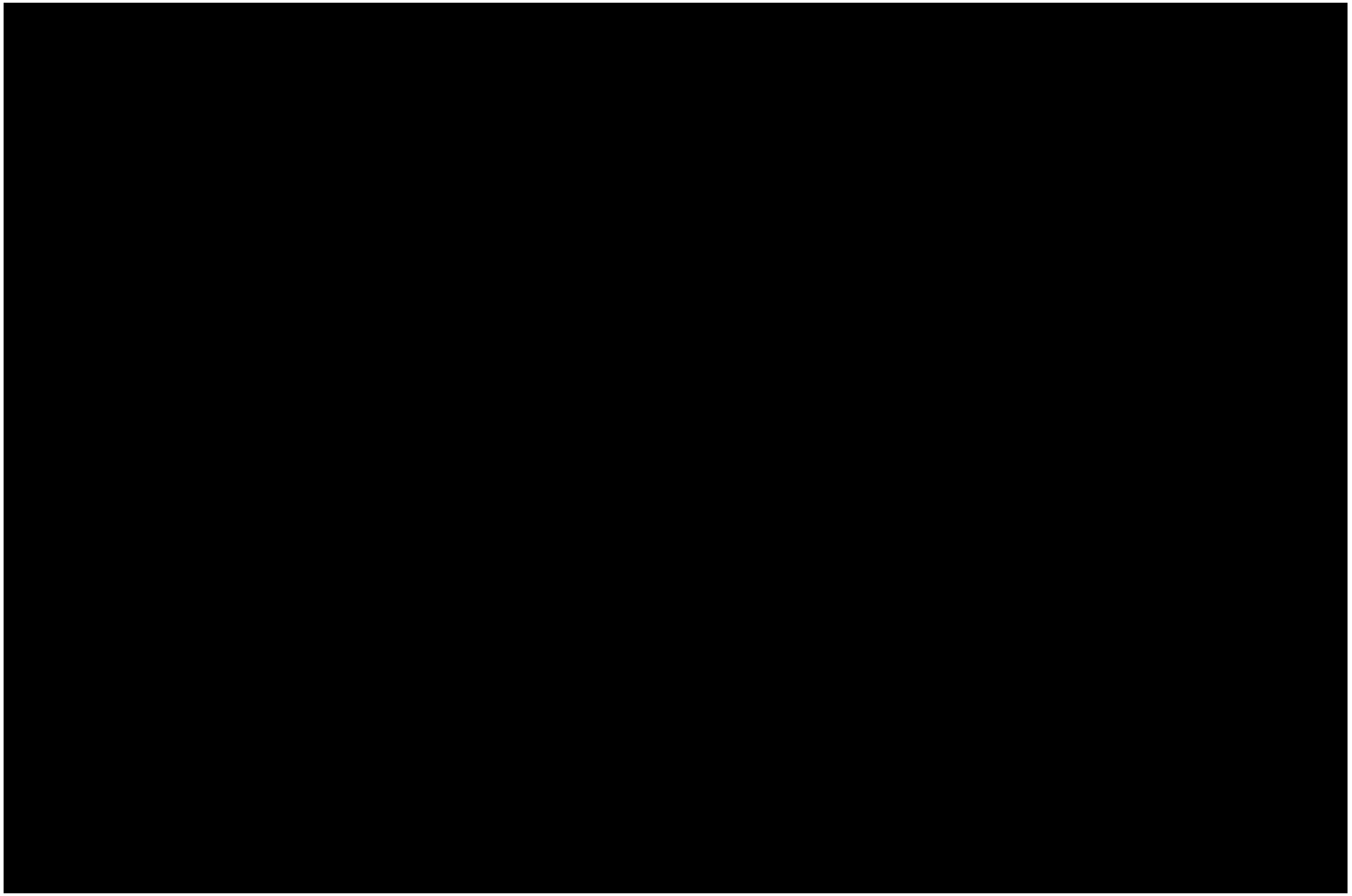
In the VISION-DMD study, pre-planned analyses of Time to stand from supine (TTSTAND) velocity for vamorolone 6.0 mg/kg/day versus prednisone were conducted for the following subgroups:

[redacted]

Please refer to Figure 1**: Forest plot TTSTAND velocity in subgroups (mITT-1 population)**

on the following page for further information on the above.

Figure 1: Forest plot TTSTAND velocity in subgroups (mITT-1 population)



Abbreviations: 6MWT – 6-minute walk test; BL – Baseline; mITT-1 – Modified intent-to-treat (Period 1); TTSTAND – Time to stand from supine; USA – United States.

A7. Please provide a summary of the prior medications received by participants in each arm of the VISION-DMD trial.

See Table 7 for a list of the prior medications received by participants in the VISION-DMD trial.

Table 7: Prior medications received by participants in each arm of the VISION-DMD trial

ATC classification level term **Preferred name**	**Vamorolone 2.0 mg/kg (N=30) n (%)**	**Vamorolone 6.0 mg/kg (N=28) n (%)**	**Prednisone 0.75 mg/kg + Vamorolone 2.0 mg/kg (N=15) n (%)**	**Prednisone 0.75 mg/kg + Vamorolone 6.0 mg/kg (N=16) n (%)**	**Placebo + Vamorolone 2.0 mg/kg (N=15) n (%)**	**Placebo + Vamorolone 6.0 mg/kg (N=14) n (%)**	**Total (N=118) n (%)**
Subjects with any prior medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACE inhibitors, plain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enalapril maleate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril dihydrate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibacterials for systemic use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibiotics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpha and beta blocking agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carvedilol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aminoalkyl ethers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diphenhydramine hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analgesics and anaesthetics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benzocaine; phenazone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaesthetics for topical use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lidocaine; prilocaine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anilides	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibiotics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nystatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tropicamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antidiarrheal microorganisms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bifidobacterium bifidum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic acid (vitamin C), plain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic acid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bacterial and viral vaccines, combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diphtheria vaccine toxoid; pertussis Vaccine acellular 5-component; polio Vaccine inact 3v (vero); tetanus vaccine Toxoid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-lactamase sensitive penicillin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phenoxymethylpenicillin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium carbonate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium phosphate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium compounds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium carbonate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium, combinations with vitamin D and/or other drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Calcium carbonate; colecalciferol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium citrate; colecalciferol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium; colecalciferol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combinations of penicillins, incl. Beta-lactamase inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amoxicillin trihydrate; clavulanate potassium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combinations of sulfonamides and trimethoprim, incl. Derivatives	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sulfamethoxazole; trimethoprim	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combinations of vitamins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic acid; colecalciferol; retinol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids, moderately potent (group II)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Triamcinolone acetonide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids, potent (group III)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Betamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fluticasone propionate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methylprednisolone aceponate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids, weak (group I)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydrocortisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzyme preparations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tilactase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fat/carbohydrates/proteins/minerals/vitamins, combinations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colostrum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First-generation cephalosporins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cefalexin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glucocorticoids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fluticasone propionate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone sodium phosphate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Homeopathic preparation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phosphorus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ubidecarenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Iron preparations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Iron polysaccharide complex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza vaccines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza vaccine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Iron trivalent, oral preparations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ferric hydroxide polymaltose complex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Local anaesthetics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proxymetacaine hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macrolides	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Azithromycin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Magnesium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Magnesium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Measles vaccine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Measles vaccine live (schwartz); mumps Vaccine live (RIT 4385); rubella vaccine live (WISTAR RA 27/3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Melatonin receptor agonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Melatonin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multivitamins with minerals	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minerals nos; vitamins nos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multivitamins, other combinations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic acid; beta carotene; curcumin; dexpanthenol; docosahexaenoic acid; fructooligosaccharides; pyridoxine; hydrochloride; retinol; riboflavin; thiamine; hydrochloride; vitamin B12; vitamin D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic acid; nicotinic acid; pantothenic acid; pyridoxine; hydrochloride; retinol; tocopherol; vitamin B12; vitamin D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multivitamins, plain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aminobenzoic acid; minerals; vitamins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic acid; calcium Pantothenate; ergocalciferol; nicotinamide; pyridoxine; hydrochloride; retinol; riboflavin; thiamine; mononitrate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic acid; cyanocobalamin; ergocalciferol; folic acid; nicotinamide; pyridoxine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic acid; nicotinic acid; pantothenic acid; pyridoxine; hydrochloride; retinol; tocopherol; vitamin B12; vitamin D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Natural opium alkaloids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oxycodone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opium alkaloids and derivatives	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACE - Angiotensin-converting enzyme; ATC – Anatomical Therapeutic Chemical; Kg – Kilogram; Mg – Milligram.
Source: VISION-DMD CSR.[1]

A8. Please provide a summary of the concomitant medications received by participants in each arm of the VISION-DMD trial during the 24 week treatment period.

See Table 8 for a list of the concomitant medications received by participants in the VISION-DMD trial 24 week treatment period.

Table 8: Concomitant medications received by participants in each arm of the VISION-DMD trial during the 24 week treatment period

ATC Classification Level Term **Preferred term**	**Vamorolone 2.0 mg/kg (N=30) n (%)**	**Vamorolone 6.0 mg/kg (N=28) n (%)**	**Prednisone 0.75 mg/kg + Vamorolone 2.0 mg/kg (N=15) n (%)**	**Prednisone 0.75 mg/kg + Vamorolone 6.0 mg/kg (N=16) n (%)**	**Placebo + Vamorolone 2.0 mg/kg (N=15) n (%)**	**Placebo + Vamorolone 6.0 mg/kg (N=14) n (%)**	**Total (N=118) n (%)**
Subjects with any concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACE inhibitors, plain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enalapril maleate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril dihydrate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perindopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aldosterone antagonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spironolactone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Alpha and beta blocking agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carvedilol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aminoalkyl ethers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diphenhydramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diphenhydramine hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaesthetics for topical use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lidocaine; prilocaine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anilides	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diphenhydramine hydrochloride; paracetamol; phenylephrine; E hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Guaifenesin; oxomemazine; paracetamol; sodium benzoate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antacids with sodium bicarbonate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alginic acid; aluminium hydroxide; magnesium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

trisilicate; sodium bicarbonate							
Antacids, other combinations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potassium bicarbonate; sodium alginate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibiotics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACE - Angiotensin-converting enzyme; ATC – Anatomical Therapeutic Chemical; Kg – Kilogram; Mg – Milligram.
Source: VISION-DMD CSR.[1]

A9. Please complete the following tables detailing-growth related outcomes not presented in the CS (Doc B).

Table 9: Height Z-score change from baseline to Week 24 (mITT-1 population)

Height Z-score change	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)	Prednisone (n=31)	Placebo (n=29)
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (SE) vs prednisone	[redacted]	[redacted]	NA	NA
95% CI vs prednisone	[redacted]	[redacted]	NA	NA
p-value vs prednisone	[redacted]	[redacted]	NA	NA
LSM difference (SE) vs placebo	[redacted]	[redacted]	NA	NA
95% CI vs placebo	[redacted]	[redacted]	NA	NA
p-value vs placebo	[redacted]	[redacted]	NA	NA

Abbreviations: CI – Confidence interval; Kg – Kilogram; LSM – Least squares mean; Mg – Milligram; mITT-1 – Modified Intent-to-treat (period 1); SD – Standard deviation; SE – Standard error.
Source: VISION-DMD CSR.[1]

Section B: Clarification on cost-effectiveness Data

Comparator

B1. Please clarify why prednisone and deflazacort were not modelled separately and then consistently combined across all outcomes using the 85:15 split to derive SoC (as done for the costs).

Efficacy data for SoC was assumed equal to natural history data. The primary source of the natural history data is the Critical Path Institute (C-Path) Duchenne Regulatory Science Consortium (D-RSC) database which contains patient level multinational clinical data for DMD. The dataset used comprised anonymised individual patient data (IPD) from 11 international data sources, including natural history studies, placebo arms of clinical trials and registry data. The patient cohort used to generate the natural history data had 80% of patients on steroids. However, natural history

data were not presented according to individual treatment arms therefore it was not possible to differentiate the natural history data according to prednisone or deflazacort usage. Clinical validation indicated that the natural history data would be broadly reflective of SoC in the UK, while noting that without knowing dosing regimens received in the natural history data it is not possible to know for certain. Additionally, although efficacy data was available in FOR-DMD, which does report efficacy data split by deflazacort and prednisone, transition data were only available for the loss of ability to rise from the floor and the loss of ability to walk. Data on these transitions are presented in supplementary information of Guglieri et al. 2022 and these indicated that there was no statistically significant difference between daily prednisone and daily deflazacort, therefore indicating that use of the same transition matrices to represent prednisone and deflazacort is justifiable.[12]

Adverse event (AE) rates were taken from the VISION-DMD trial since this directly compared vamorolone and prednisone. Given the paucity of data, it was considered more appropriate to compare randomised data rather than use an indirect comparison between FOR-DMD and VISION-DMD. Prednisone is the most widely used glucocorticoid in the UK and deflazacort should only be used in patients in whom oral prednisone is not tolerated due to cushingoid side effects.[13] To explore uncertainty, a scenario is provided in response to Question B8 which uses deflazacort AE rates using deflazacort data taken directly from FOR-DMD.

By contrast, it was possible to weight the steroid cost data according to usage, with the proportion of patients split across prednisone and deflazacort which was based on a burden of illness study with 84% on prednisone.[14]

Model Structure

B2. Besides model structures based on ambulatory and ventilation status (Model II and III), Landfeldt 2017 also included Model I based on patient reported outcome DMD functional ability self-assessment tool (DMDSAT) and further indicated: "…DMDSAT exhibits excellent psycho-metric properties and have been shown to have good clinical validity and is currently the only tool that measures functional ability across the entire trajectory of disease…".

Please explain why a model structure with health states based on DMDSAT was not considered.

Ambulation status was considered to best reflect the progression of DMD since it reflects the goal of treatment, which is to delay or, potentially in the future, prevent the decline of muscle strength and loss of functional abilities. The Project HERCULES model represents a step change in the approach to economic modelling of DMD. The Project HERCULES model also provides a more detailed picture of the course of disease after the loss of ambulation. In addition to health states capturing a patients' ventilation status, the loss of hand-to-mouth function (HTMF) is also captured.

Although DMDSAT has been shown to have good clinical validity, it suffers from limitations, including subjectivity, since it relies on self-reporting by patients or their caregivers which can introduce variability in assessments.[15] DMDSAT may also not be sensitive enough to detect subtle changes in disease progression, particularly in the early stages of DMD.[15] Ambulatory health states were specifically considered as they are resource intensive and are associated with decreased utility.

B3. When the 'Transfer state' is excluded in the model [using 'Natural history' sheet, Include Transfer state? (Cell B34)], the state membership changes to zero in other health states as well i.e., for State 4 to 9 and a substantial increase in ICER has been noted. Please clarify and provide further explanation as needed.

The model developed under Project HERCULES was designed to be used for a range of possible future DMD treatments coming to market, therefore the model includes functionality for a range of data sources and treatment types. Due to tight timelines, some functionality was not stripped from the model for this submission. The inclusion of the transfer state marks a key departure from previous models and was identified during model development by patients, caregivers, and clinicians as a key milestone in the progression of DMD, with an impact on both quality of life and resource use. An option was included in the Project HERCULES model with functionality to exclude the transfer state in case data became available to model this, however to the company's knowledge there are currently no natural history data

to inform the model if this state is excluded. Therefore, the 'Include Transfer state?' switch is not functional in the current model and should not be used.

Mortality

B4. Table 46 in the CS mentioned that the hazard ratio for State 3 (transfer) was assumed the same as State 4 (HTMF, no ventilation). Please explain the rationale behind this assumption. Also, elaborate why it was not assumed the same as State 2 (late ambulatory) instead of State 4 (HTMF, no ventilation).

The title of this section is 'Mortality', however, the company would like to clarify that these data relate to health state transitions for the 'No treatment' arm relative to the SoC arm, as opposed to mortality data.

This assumption was made due to lack of data for the transfer health state. Hazard ratios (HR) were available from McDonald et al.[16] for the late ambulatory health state (2.41), the HTMF, no ventilation health state (1.41), and the no HTMF, no ventilation health state (1.16). McDonald et al. reported KM analyses of time to ambulatory milestones in DMD patients, split by patients who were on-treatment with glucocorticoids for over 1 year, and those who were on glucocorticoid treatment for <1 month or were never treated. The paper used data from the CINRG registry recorded between 2006 and 2016. Milestones that aligned to model health states (age at loss of HTMF, age at loss of ability to stand from supine, and age at loss of ambulation) were digitized and cox-proportional hazard analysis conducted to generate a HR for the ≥1 year and <1-month steroid use arms. The HR for the transfer health state was assumed the same as State 4 (HTMF no ventilation). Table 10 presents the impact of using the following alternative assumptions:

- Same HR as to state 2 (late ambulatory).
- Average of HR to state 2 (late ambulatory)' and HR to state 4 (HTMF, no ventilation).
- Average of To state 2 (late ambulatory)', 'To state 4 (HTMF, no ventilation)', and 'To state 5 (no HTMF, no ventilation)'.

The results demonstrate that the ICER is robust to the HR used for this health state. Of the approaches shown below, the base case represents the most conservative approach.

Table 10: Scenario analyses of different assumptions for State 3 (transfer) mortality hazard ratio

Scenario	Hazard ratio	Incremental costs	Incremental QALYs	ICER
Base case	1.41	[redacted]	[redacted]	£29,799
Assume the same as 'To state 2 (late ambulatory)'	2.41	[redacted]	[redacted]	£28,318
Average of 'To state 2 (late ambulatory)' and To state 4 (HTMF, no ventilation)'	1.91	[redacted]	[redacted]	£28,925
Average of 'To state 2 (late ambulatory)', 'To state 4 (HTMF, no ventilation)', and 'To state 5 (no HTMF, no ventilation)'	1.66	[redacted]	[redacted]	£29,324

Abbreviations: HR – Hazard ratio; HTMF – Hand-to-mouth function; ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life year.

Transition probabilities

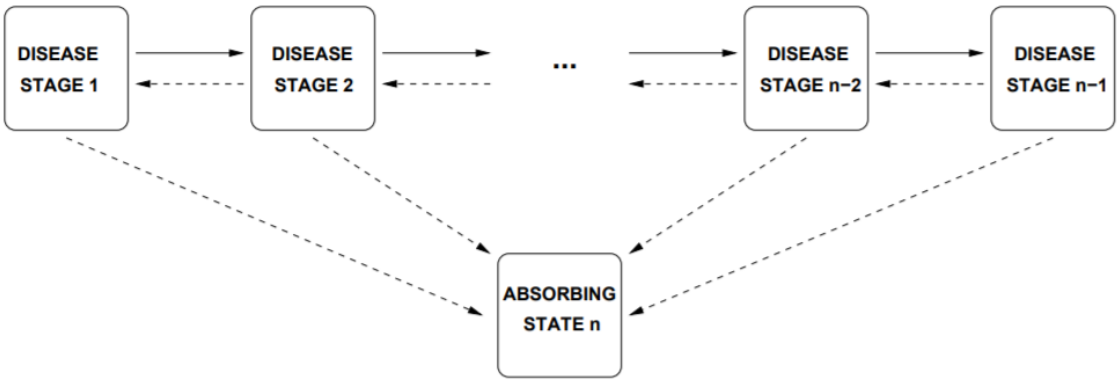
B5. When 'use simple transition probabilities' is unchecked in the model [using 'Natural history' sheet, Use simple transition probabilities? (Cell B33)], no impact on the results was observed. The note on the model says see report for more details on the full and simple methods. However, EAG was not able to find any such explanation in the CS. Please provide detailed explanations on the simple and full method for transition probabilities and clarify whether the full method has been implemented or not in the model.

The model developed under Project HERCULES was designed to be used for any future DMD treatment coming to market, therefore the model includes functionality for the full method for transition probabilities. Due to tight timelines, some model functionality including functionality for full transition probabilities was not stripped from the model for this submission. The report referred to in the model is the technical report of the original model rather than the CS. The full method for transition probabilities has not been implemented in the submitted model, but is described in full below in addition to the simple method for transparency.

Transition intensities from the NHM were converted into transition probabilities to determine health state membership over time for SoC. Figure 2 presents a general

model for disease progression.[17] Here, matrix Q represents the matrix of transition intensities.

Figure 2: General model for disease progression



$$Q = \begin{pmatrix} q_{11} & q_{12} & 0 & 0 & \dots & q_{1n} \\ q_{21} & q_{22} & q_{23} & 0 & \dots & q_{2n} \\ 0 & q_{32} & q_{33} & q_{34} & \ddots & q_{3n} \\ 0 & 0 & q_{43} & q_{44} & \ddots & q_{4n} \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 0 \end{pmatrix}$$

A proportional hazards model was assumed, where each element in the transition intensity matrix was defined by:

$$q_{rs}\big(z(t)\big) = q_{rs}^{(0)} \exp\big(\beta_{rs}^{T} z(t)\big),$$

where $z(t)$ is a vector of the covariates and β_{rs} is a vector of the coefficients.[17]

The matrix of transition intensities was transformed into a transition-probability matrix. Formally, this is done using the formula:

$$P(t) = \exp(Qt) = \sum_{n=0}^{\infty} Q^n \frac{t^n}{n!}$$

Where *t* is the cycle length in the model.[18]

This formula allows for the fact that multiple transitions may occur within a cycle, meaning patients may 'skip' a health state in the model. However, this formula is difficult to evaluate in Microsoft Excel® and adds to the complexity of the model, making it more difficult to adapt. To address this, the model utilises simplified transition probabilities. Using this option, the probability of transitioning from state i to state j is calculated according to the formula[19]:

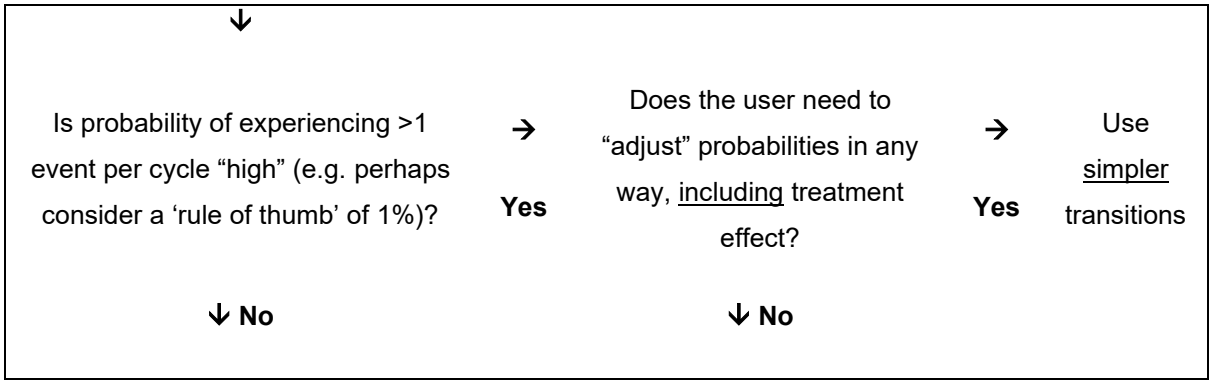
$$p_{i,j} = \frac{q_{i,j}\left(1 - \exp\left(-\sum_{r \neq i} q_{i,r}\right)\right)}{\sum_{r \neq i} q_{i,r}}.$$

Here $p_{i,j}$ 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. Using the simplified transition probabilities, as in this submission, patients are only able to move to the next health state or the death state. This simplified probability method does not allow for multiple transitions to occur during the same cycle.

Advantages of the simplified method are that it reduces the computational burden and is more amenable to adaptation. For example, age-dependent hazards and custom treatment effects are easily incorporated into the simplified probabilities. The primary disadvantage is that it may understate the rate of disease progression by failing to allow for multiple transitions in a cycle.

During review of the model by an external consultancy, the reviewers were asked to comment on the choice between the simplified and full set of transition probabilities. They suggested that following the algorithm in Figure 3 may aid users in making this choice. As the transition probabilities are adjusted for the 'No treatment' arm, this indicates the simple method for transition probabilities is appropriate.

Figure 3: Suggested decision process concerning choice of transitions set



Use simpler transitions	Use full set of transitions

B6. In the CS, Doc B, Section B.3.2.2, it has been mentioned: "No data were available on the transitions to and from the Transfer state; instead, this was informed by data from an elicitation exercise".

i. Please provide more information on this elicitation exercise (especially, what data were collected in the elicitation exercise and how it was used to inform the transition probabilities).

Where little or no data were available to inform transitions in the model, such as with the transfer state, an elicitation exercise was conducted by the University of Leicester, details of which have been previously published.[20] This included an initial pilot, in which information was elicited from four clinicians and four caregivers involved in the Project HERCULES collaboration. This was followed by an online survey of 20 Duchenne UK stakeholders, including healthcare practitioners, parents, and caregivers. The anonymised online survey was circulated by Duchenne UK and received 20 responses. Respondents were all from the UK and included:

- Two "medically qualified" respondents.
- Twelve "parent" respondents.
- Two "parent and carer" respondents.
- One "parent and nurse" respondents.
- Three "patient" respondents.

Using a questionnaire, respondents were asked to describe the average age at which patients enter and exit health states (Table 11). From the responses received, the mean age and standard deviation (SD) for entering and exiting the states was estimated and used to generate pseudo IPD from which transition intensities could be estimated. Where some transitions were observed in the D-RSC dataset, the pseudo IPD were used to augment rather than replace these data. This exercise was also used to inform transitions into health state 4 (HTMF, no ventilation), 5 no HTMF, no ventilation) and 6 (HTMF, night-time ventilation).

Table 11: 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] 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] 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: On average, how long do you think it would be before they lost either HTMF or required night-time ventilation? (or say, on average, at what age you think this would happen, if that is easier) [state 4 to state 5 or 6] Can you specify a plausible range for this average? 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; M = Metre.
Note: what we mean by a plausible range – lower value is such that 1 in 4 (25%) patients would be below it, and upper value is such that 1 in 4 (25%) patients would be above it.

For both the pilot study and subsequent online survey, 50 hypothetical patients were generated in state 3 (transfer state) with starting ages simulated from a normal distribution, with the mean equal to the mean age of answers to Question 1, and SD selected such that 50% of the normal distribution covered the mean age range of answers in Question 1. Their transition times to state 4 (HTMF, no ventilation) were simulated by taking their age in state 3 (transfer state) and adding a random value from a normal distribution with the mean equal to the mean difference between Question 1 and Question 2, and a SD selected in the same way as for state 3 (transfer state). This value was left-truncated at 0.1 years and right-truncated at 15 years. This was repeated for transitions from state 4 (HTMF, no ventilation) to state 5 (no HTMF, no ventilation)/state 6 (HTMF, night-time ventilation) with these transitions apportioned to state 5 (no HTMF, no ventilation) and state 6 (HTMF, night-time ventilation) based on responses to the final part of Q3.

ii. Also, Broomfield 2020 mentioned that further elicitation would be necessary to reduce the uncertainty around transitions in and out of Transfer state and identified the need for future data collection around transfer state in clinical studies. Please explain what was done further to

reduce this uncertainty and include details about any further data collection in this regard.

No additional detail on further elicitation was available from the authors of the Project HERCULES model. The best available data were provided in the submitted model.

Treatment effect duration

B7. Please explain why changing the duration of treatment effect (years) in the model ('Clinical data' sheet, Cell D67), has no impact on the results.

Cell D67 in the clinical data sheet represents the hazard ratio for mortality for vamorolone versus SoC. This hazard ratio is 1.00 in the submission base case therefore there is no treatment effect and no subsequent impact when changing the duration of treatment effect. When the hazard ratios are amended from 1.00, the duration of treatment effect value has a varying impact on the ICER. Similarly to the response to Question B5, this functionality was part of the original Project HERCULES model but is not required for vamorolone given vamorolone equivalence to full-dosed steroids.

Adverse events

B8. As per Table 43 of CS (Doc B), SoC comprises both prednisone and deflazacort and a split of 85:15 has been used in the model. However, the moderate to severe AESI and acute event rates were provided only for prednisone and not for deflazacort. Please clarify. Also, if the event rates are available for deflazacort please include in the model and reweight the AE rates based on 85:15 split to align with the SoC definition.

AESI rates were provided only for prednisone since prednisone is predominantly used in UK clinical practice. When including the moderate/severe AESI rates for deflazacort from the full trial period of FOR-DMD (36 months of follow-up), the ICER increases slightly to £30,544. AESI rates used in this scenario are shown in Table 12. Cost-effectiveness results of this scenario are shown in Table 13.

Table 12: FOR-DMD AESI and acute event rates – deflazacort[21]

AESI	Deflazacort 90 mg/kg (N=56) n (%); f (%)

Weight gain	0
Behavioural issues	5 (8.9); 11 (19.6)
Cushingoid effects	2 (3.6); 3 (5.4)
Immune supressed/infection	9 (16.1); 14 (25.0)
GI symptoms	2 (3.6); 3 (5.4)
Diabetes	1 (1.8); 1 (1.8)
Skin/Hair change	0

Abbreviations: AESI – Adverse event of special interest; GI – Gastrointestinal; Kg – Kilogram; Mg – Milligram; N = Total patient count in the group; n = Patient count for AE.
* Indicates events for which no data were available; in this case, the average rate ratio was used.

Table 13: Cost-effectiveness results including deflazacort AESI rates

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,544**

Abbreviations: ICER - Incremental cost-effectiveness ratio; LYG - Life years gained; QALY - Quality-adjusted life year; SoC – Standard of care.

B9. AESI and acute event rates (24 weeks) as per Table 48 and Table 49 in the CS, indicated higher rate for placebo compared to prednisone for pyrexia. Please explain any potential reasons for the same.

Prednisone can suppress inflammation and therefore hide pyrexia. Therefore, the reported rate of pyrexia in VISION-DMD was lower than might be expected when comparing to placebo.[22]

B10. The CS stated that stunted growth data were not available either in VISION-DMD or FOR-DMD and were taken from literature. However, this was only applied to SoC arm and not Vamorolone i.e., 0% assumed for Vamorolone. Please justify this assumption.

At Week 24 of the VISION-DMD study, the change from baseline in height percentile for vamorolone 6.0 mg/kg was 3.86.[2] In contrast, the change from baseline in height percentile for prednisone was -1.88.[2] At Week 24, the change from baseline in height Z-score was 0.18 for vamorolone 6.0 mg/kg.[1] These results demonstrate that the height of patients receiving vamorolone was not stunted and therefore an assumption of 0% stunted growth is appropriate. This change from baseline data was not available for placebo, but reduced growth and short stature are common clinical manifestations of DMD even in the absence of steroid therapy.[23] Therefore, stunted growth was applied to the SoC arm but not to the vamorolone arm.

B11. Please clarify how the rate of behavioural issues reported in Table 48 of the CS (Doc B) for prednisone ([redacted]) was derived, as it does not seem to align with the trial data ([redacted] as per Table 72, VBP15-004 CSR).

These data describe the rate of moderate to severe AESIs, reporting the number of events rather than the number of patients. See Table 14 for full results in this format, copied from Table 14.2.3.16a.1 of the CSR (Clinically relevant TEAEs of special interest by AESI group and PT), with the value of interest **highlighted**.
Moderate/severe AEs in the VISION-DMD trial in period 1 were equal to clinically relevant AEs by definition. Since there were no mild AEs leading to discontinuation or reported as an SAE, all clinically relevant AEs were moderate to severe AEs.

Table 14: Moderate to severe AESI (SAF-1, VISION-DMD trial)

AESI category	Placebo (N=29) n (%); f (%)	Prednisone 0.75 mg (N=31) n (%); f (%)	Vamorolone 2.0 mg (N=30) n (%); f (%)	Vamorolone 6.0 mg (N=28) n (%); f (%)
Any AESI	5 (17.2); 5 (17.2)	11 (35.5); 15 (48.4)	2 (6.7); 5 (16.7)	1 (3.6); 1 (3.6)
Behaviour problems	1 (3.4); 1 (3.4)	7 (22.6); 8 (**25.8**)	1 (3.3); 1 (3.3)	-
Cushingoid features	-	-	-	1 (3.6); 1 (3.6)
Diabetes related conditions/labs	-	-	-	-
Gastrointestinal symptoms	1 (3.4); 1 (3.4)	1 (3.2); 1 (3.2)	-	-
Hypertension	-	-	-	-
Immune / infections	3 (10.3); 3 (10.3)	4 (12.9); 4 (12.9)	2 (6.7); 4 (13.3)	-
Skin/hair changes	-	1 (3.2); 1 (3.2)	-	-
Weight gain / increased appetite	-	1 (3.2); 1 (3.2)	-	-

Abbreviations: AESI – Adverse event of special interest; F – AE case count; Kg – Kilogram; Mg – Milligram; N = Total patient count in the group; n = Patient count for AE.
Source: ISS outputs Table 14.2.3.16a Clinically relevant TEAEs of Special Interest.

Utilities

B12. Table 42 and Section B.3.4.5 of the CS mentioned that EQ-5D data were collected in VISION-DMD trial but lacked sensitivity, however, section B.3.4.1 mentioned that EQ-5D data were not available from the VISION-DMD trial.

Please clarify this inconsistency. Also, if EQ-5D data were collected in the trial please include a scenario in the model using trial EQ-5D derived utility values.

Please see response to Question A1. No EQ-5D data were available in VISION-DMD, therefore it is not possible to include this in the model.

Uncertainty

B13. The model did not have a scenario analysis sheet and it was not clear to EAG what settings were used for some of the scenarios. Please elaborate the model settings for all the scenarios (especially for scenarios 4, 5, 8, 15 and 16, as EAG was unable to replicate the results for these scenarios).

Switches on the settings sheet have been added for ease to display how to replicate the results for scenarios 4, 5, 8, 15 and 16 from the base case model. The switch in cell D36 allows the user to switch between either 'All down-titrate to 4mg' option for scenario 4, or 'Half down-titrate to 4mg' option for scenario 5. The switch in cell D38 of the Settings sheet can be changed to 'AESI' to select scenario 8 and use AESI of all grades, rather than only moderate to severe AESI. Scenarios 15 and 16 can be selected by the switch in cell D40 of the same sheet allowing the selection of either 'Loss of HTMF' for scenario 15, or 'Starting at full time ventilation' for scenario 16.

Model validation

B14. The model predicted QALYs for SoC arm in the base case ([redacted]) were found to be lower than that observed in Agboola 2020 (6.88 for prednisone and 8.40 for Deflazacort) and Landfeldt 2017 (SoC patient QALYs as per Model II – 7.17 and Model III – 5.96). Please explain why the predicted QALYs are comparatively lower (versus Landfeldt 2017, especially) for SoC.

The model predicted QALYs for the SoC arm in the base case were lower than that observed in the literature because the model includes carer disutilities. The Agboola model did not include caregiver disutility and the Landfeldt model presents patient and caregiver QALYs separately. In the base case, carer QALYs are -1.31 therefore the SoC patient QALYs is 6.88, which aligns with Agboola 2020 and Landfeldt 2017.[24,25]

B15. The predicted QALYs for 'no treatment' based on the submitted model was [redacted] (as reported in 'Engine_3' sheet, Cell EI2), higher than that of SoC ([redacted]). This implies that SoC as per current UK clinical practice is worse than 'no treatment' which sounds unrealistic. Please explain this discrepancy.

Patients and caregivers both endure increased levels of disutility due to patients receiving steroidal treatment. This is seen in the increased levels of adverse events and acute events due to treatment and the subsequent impact this has on their caregivers (e.g., increased behavioural impact). This consequently reduces the overall QALYs anticipated for patients receiving SoC in comparison to those receiving 'no treatment'.

Additionally, the treatment arm described as 'no treatment' is not considered a formal comparator arm in the model. The no treatment arm has been included simply to model transitions for patients who have discontinued active therapy or are on a suboptimal dose of steroids. The company encourages the EAG to interpret the no treatment arm with caution.

EAG additional company clarification questions

The CS DOC B (Section B.3.3.5) mentioned: "Decision Support Unit (DSU) Technical Support Document (TSD) 14 states to attempt survival analysis using six standard parametric curves: exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma. This was attempted, however, given the small patient numbers, the parametric curves produced implausible results. Exponential curves were therefore fitted to the above data points and are used in the model base case, given this is the simplest parametric model"

Could you please provide the parametric curves attempted (other than exponential) along with the associated parameters, for which the results were judged to be implausible?

Parametric models were attempted as part of the original submission development, however, the models gave implausible results and due to time constraints, it was not possible to resolve these ahead of submission, hence the submitted model contained an Excel-based exponential distribution. Since submitting, the company has been able to identify the issue and appropriately parametrise the VISION-DMD

vamorolone data. Figure 4 depicts Kaplan-Meier (KM) data for the vamorolone 6.0 mg/kg/day arm of the VISION-DMD trial in period 1 and 2, while Figure 5 presents the six parametric distributions compared to the KM data. The parameters of the six parametric curves (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma) are presented in Table 15.

Figure 4: VISION-DMD, vamorolone 6.0 mg/kg/day, period 1 and 2 - Kaplan-Meier data

Abbreviations: Kg – Kilogram; Mg – Milligram.

Figure 5: VISION-DMD, vamorolone 6.0 mg/kg/day, period 1 and 2 - Kaplan-Meier data with extrapolation curves

Abbreviations: Kg – Kilogram; KM – Kaplan-Meier; Mg – Milligram.

Table 15: VISION-DMD, vamorolone 6.0 mg/kg/day, period 1 and 2 - parametric curves

Function	Parameter	Coefficients	SE	Covariance			AIC	BIC
Exponential	rate	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Gompertz	shape	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Log-logistic	shape	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Log-normal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Generalised gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; Kg – Kilogram; Mg – Milligram; SE – Standard error.

Considering model fit based on Akaike information criterion (AIC) / Bayesian information criterion (BIC) values in Table 15, all curves except for generalised gamma fit the data similarly well. To aid with curve selection, the extrapolations were compared against data from the vamorolone Expanded Access Programme (EAP) described in the CS [Document B, B.2.11. (page 88)]. As displayed in Figure 6, the EAP indicates an earlier drop than data from VISION-DMD which suggests the exponential and log-normal may not give appropriate long-term extrapolations, as these curves do not meet the EAP KM curve until beyond three years. As the log-logistic curve represents a mid-point of the extrapolations and joins the EAP curve at a similar timepoint to the Weibull and generalised gamma curves, it was considered that log-logistic curve is a reasonable curve to use for the model base-case.

Figure 6: Extrapolation curves compared to EAP Kaplan-Meier data

Abbreviations: EAP – Early Access Programme; KM – Kaplan-Meier.

Additionally, as mentioned in the original submission, due to the time constraints it was not possible to extrapolate CINRG data as part of the original submission. It has now been possible to model these data and results are presented below. KM data for prednisone and deflazacort are displayed alongside their extrapolation distributions in Figure 7 and Figure 8, with coefficients in Table 16 and Table 17, respectively. The Gompertz distribution was not included within the prednisone or deflazacort distributions due to the models being unable to converge for either treatment. The difference in KM curves between prednisone and deflazacort may be attributed to deflazacort often being used as a second-line treatment post-prednisone, where

discontinuation would be less prevalent due to no further treatment options being available. The concerns which initially cause patients to discontinue from prednisone, such as weight gain or bone density, would be less impactful on discontinuation with deflazacort due to lack of additional treatment options for patients to transition to.

Figure 7: CINRG Prednisone - Kaplan-Meier data with distribution curves

Abbreviations: KM – Kaplan-Meier.

Figure 8: CINRG Deflazacort - Kaplan-Meier data with distribution curves

Abbreviations: KM – Kaplan-Meier.

Table 16: CINRG, Prednisone - parametric curves

Function	Parameter	Coefficients	SE	Covariance			AIC	BIC
Exponential	rate	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]			
Log-logistic	shape	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]			
Log-normal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]			
Generalised gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; SE – Standard error.

Table 17: CINRG, Deflazacort - parametric curves

Function	Parameter	Coefficients	SE	Covariance			AIC	BIC
Exponential	rate	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]			
Log-logistic	shape	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]			
Log-normal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]			
Generalised gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; SE – Standard error.

Considering model fit based on AIC/BIC values, all curves fit the prednisone data similarly well, and all curves except for exponential fit the deflazacort data reasonably well. In line with recommendations from Technical Support Document 14[26], the log-logistic model was applied to both the prednisone and deflazacort arms for consistency with the vamorolone arm.

The cost-effectiveness model has been updated to reflect the curves for vamorolone prednisone and deflazacort; Table 18 and Table 19 present the model results updated to reflect the new data, using the vamorolone proposed PAS price and list price, respectively. The company propose that this should be the updated base case to use for the appraisal.

Table 18: Cost-effectiveness results using updated extrapolations for vamorolone, prednisone and deflazacort, vamorolone proposed PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,221

Abbreviations: ICER - Incremental cost-effectiveness ratio; LYG - Life years gained; QALY - Quality-adjusted life year; SoC – Standard of care.

Table 19: Cost-effectiveness results using updated extrapolations for vamorolone, prednisone and deflazacort, vamorolone proposed list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER - Incremental cost-effectiveness ratio; LYG - Life years gained; QALY - Quality-adjusted life year; SoC – Standard of care.

Also, Table 77 stated that the exponential curve produced initially implausible long length of stay in state 8A/8B and so a piecewise exponential was implemented later. However, it is not clear to EAG whether similar attempts were made with other parametric fits before they were judged to produce implausible results. Please clarify

As part of the original DMD Project HERCULES development, once the model structure (health states) had been agreed and data identified, transition intensities were estimated via the following six steps. (1) The mean age of patients observed in each state in the D-RSC dataset was estimated. (2) A piecewise constant hazard function was fitted to the mortality data, with cut points determined by the mean age in each state, to estimate the mortality rate for 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 rates being equal to four decimal places. An exponential distribution (i.e., constant transition intensities) was used to fit the multistate model for transitions up to state 8A/8B. A piecewise exponential distribution was assumed for transitions from state 8A/8B to state 9 (death). Initial consideration of the exponential distribution for all transitions led to an implausibly long length of stay in state 8A/8B. This was due to the long tails associated with the exponential distribution and a fixed mortality rate. Use of the piecewise exponential facilitated implementation of an increased rate of mortality after age 30 years in state 8A/8B.

The exponential distribution was used to fit the multistate model from states 1 to 8A/8B due to its ease of interpretation and because sparse data means that other models, for example a Weibull model, were less likely to converge. The exponential distribution results in long tails in the extrapolations of health state occupancy, leading to a small probability of implausibly long time periods in affected health states. Initial analysis assuming an exponential distribution for all transitions led to an implausibly long mean length of stay in state 8A/8B. Therefore, a piecewise exponential was assumed for transitions out of state 8A/8B to death, which resulted in more plausible predictions of the mean length of stay in state 8A/8B.

Section C: Textual clarification and additional points

C1. Table 39 reported QALYs for treatment based on Model III as 6.93, whereas it is 6.39 as per the Landfeldt 2017 publication (Table 2). Please clarify.

The QALYs reported in Table 39 of the CS are incorrect. This value should be 6.39 as is detailed in Landeldt 2017.

C2. Can you confirm that the intervention terms in the main Embase and Medline searched ('vamorolone'/syn OR 'steroid'/exp) were only thesaurus terms? If so, why were no free text terms used?

The intervention terms searches were only thesaurus terms. No free text terms were used as scoping searches suggested that using these search strategies would identify all potentially relevant information.

C3. Why were different comparator terms used in the Cochrane and Embase/Medline search, and why was the main comparator, prednisone, not used in either?

Searches were an update of previous search strategies used. The Cochrane search should have only included vamorolone and steroids, as per the Embase/Medline search, as idebenone and ataluren are not comparators of interest within this submission; any studies of these interventions were excluded. Prednisone inclusion is covered by searching for steroids.

C4. Was the same search strategy used in all iterations of the economic searches (i.e. in the "initial review", "updated review" and "targeted search", as described in the PRISMAs in Appendix G)? If the searches differed, can you describe how?

The same search strategy was used in all iterations of the economic searches.

C5. Why was the International Clinical Trials Registry Platform (ICTRP) not searched?

All relevant published information will have been identified using the databases and conferences searches listed, that is:

- EMBASE (covers biomedical literature from 1974 to present).
- MEDLINE and MEDLINE In-Process (covers journals from 1966 to present); EMBASE interface.
- EconLit (via OvidSP interface).
- ScHARRHUD.
- EuroQoL.
- Cochrane Central Register of Controlled Trials (Central) (Cochrane Library).

- Muscular Dystrophy Association Scientific Conference.
- International Annual Congress of the World Muscle Society.
- Supplementary searches of “grey” literature in Google Scholar and through the NICE and Scottish Medicines Consortium (SMC) websites. Furthermore, searches included clinicaltrials.gov, searches of the manufacturer’s repository of evidence, websites of manufacturers of comparator products, and bibliographic searching of any SLRs identified during screening.

C6. In document B, Table 18 and Table 20 refer to “LSM difference (SE) vs placebo”. Can the company confirm this should actually be “LSM difference (SE) vs prednisone” for these tables?

Correct, this is an error in the submission and should be “LSM difference (SE) vs prednisone”.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vamorolone for treating inflammation associated with Duchenne muscular dystrophy [ID4024]

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

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 charity organization 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 organization is dedicated to improving the lives of those with DMD through research, advocacy, and support. Action Duchenne is funded by donations, community fundraisers, grants, and sponsorships from pharmaceutical companies. Number of staff: twelve.
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.] **If so, please state the name of the company, amount, and purpose of funding.**	£10,000 sponsorship funding received from Santhera Pharmaceuticals (Switzerland) Ltd towards 2023 Action Duchenne's International Conference The funding is not ongoing. The purpose of funding is not related to Vamorolone for treating inflammation associated with Duchenne muscular dystrophy [ID4024]. With the support from our sponsors and exhibitors, the charity is able to offer free conference tickets to all UK and international Duchenne families.

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?	Action Duchenne collaborated with other DMD patient organisations MDUK and Duchenne UK in producing this submission. There are three main sources of information:
	• Project HERCULES, a Duchenne UK-led international collaboration to develop evidence and tools to support HTA for new products for DMD. In particular:
	  ○ 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
	  ○ The burden of long-term corticosteroid use in the treatment of Duchenne Muscular Dystrophy in the UK, Tolley et al, Value in Health, Dec 2022, https://www.valueinhealthjournal.com/article/S1098-3015(22)04283-8/fulltext
	  ○ 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
	• A 2020 survey conducted in collaboration with Pathfinders UK, Alex's Wish, Action Duchenne, Duchenne Family Support Group and Muscular Dystrophy UK recording the experiences of DMD patients. This was in preparation for the eventually discontinued NICE idebenone appraisal (ID1092) [GID-TA10310].
	• A survey of our community in August and September 2023 specifically on steroids, which asked respondents if they had taken part in a vamorolone trial

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 live male births in the UK. Patients generally exhibit symptoms between one and three years of age. There is no newborn screening program 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. The diagnosis of DMD is devastating for a family and there is often very little psychological support for them to come to terms with the diagnosis. Caregivers often suffer with depression and anxiety after diagnosis and have prolonged absences from work. Because of the progressive nature of the disease, the depression and anxiety continue as muscle function is lost - both for patients and their caregivers. 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. 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 may have learning disabilities or neurological disorders such as autism or learning disabilities. These usually remain static and do not worsen as DMD progresses. 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

[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

	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] 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-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) Standard medical management of DMD requires consideration of the use of corticosteroids as well as respiratory, cardiac, orthopaedic, and rehabilitative interventions (see section 7). The potential for corticosteroids was published in 1989 in a randomized, 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. The Finding the Optimum Regimen for Duchenne muscular dystrophy (FOR DMD) study compared three ways of giving corticosteroids to boys with DMD to determine which of the three ways increased muscle strength the most, and which causes the fewest side effects. This study was published in 2022[3], and reported that treatment with daily prednisone or daily deflazacort, compared with intermittent prednisone alternating 10 days on and 10 days off, resulted in significant improvement over 3 years in a composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment; there was no significant difference between the 2 daily corticosteroid regimens. The findings support the use of a daily corticosteroid regimen over the intermittent prednisone regimen tested in the study as initial treatment for boys with DMD. Steroids also have severe and very detrimental side effects that hugely impact on quality of life. Experiences of these side effects are elaborated on in section 6, but include: • serious effects on bone health leading to excess fractures which can cause pain and speed up the loss of muscle function • extreme weight gain

[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

[3] Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular DystrophyA Randomized Clinical Trial, Guglieri et al, JAMA, Apr 2022

	• adrenal insufficiency and crisis (if not administered correctly) • stunted growth, which causes psychological pain • delayed puberty and associated psychological challenges • behavioural problems.
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. There is no approved treatment which treats the underlying causes of DMD. Project HERCULES commissioned a study to gather qualitative evidence from patients and their parents on the adverse impact of long-term, high-dose steroid use side effects in DMD.[5] This found five prominent themes reported by the focus group; • **Physical appearance.** Physical appearance was a topic of high concern to both patients and parents and impacted on other areas including mental health, usual activities, and ability to "fit-in" socially. Main concerns were weight gain, short stature, and cushingoid appearance, all contributing to patients looking younger than their peers, which often resulted in them being treated differently. • **Delayed puberty.** Corticosteroids taken long-term can delay puberty, leading to a multitude of physical and mental complications. Testosterone is prescribed by some clinicians to induce puberty but parents reported that it was a challenge to get this prescribed and that response in those receiving it was varied. Patients reported that delayed puberty made them feel self-conscious and socially-isolated. • **Adrenal Crisis.** Patients taking long-term, high-dose corticosteroids are unable to produce heightened levels of cortisol required during times of physiological stress risking adrenal crisis, a life-threatening situation. Parents found this a huge burden as often emergency services are not trained to recognise the symptoms. Furthermore, schools may not be able to administer the injection and, instead, have to wait for a paramedic to arrive, meaning parents felt a need to always be near-by in case their child was injured/ ill so that they could explain the risks and make sure that the appropriate care was provided. • **Mood and behaviour.** Some of the parents felt that after starting steroids their child's behaviour changed drastically, with one parent describing it as the biggest burden they had experienced as a caregiver. HCPs reported that this is highly variable however existing neurodevelopmental conditions may be a factor in how a

[4] Diagnosis and management of Duchenne muscular dystrophy, part 1, Birnkrant et al, Lancet Neurology, Mar 2018, https://pubmed.ncbi.nlm.nih.gov/29395989/

[5] The burden of long-term corticosteroid use in the treatment of Duchenne Muscular Dystrophy in the UK, Tolley et al, Value in Health, Dec 2022, https://www.valueinhealthjournal.com/article/S1098-3015(22)04283-8/fulltext

	child responds emotionally and behaviourally when starting corticosteroid treatment. Several patients reported suffering with anxiety and low mood, however it is very difficult to ascertain how much is attributable to their condition, and whether taking a steroid exacerbates this or not. Both families and HCPs said there is not enough specialist psychological support available. • **Bone density.** Long-term corticosteroid use can reduce bone density leading to an increased risk of bone fractures. Both patients and parents reported this as being of high concern as it was linked to increased risk of adrenal crisis and worries over not being able to walk again and becoming non-ambulatory sooner. The study reported that an online survey, circulated via patient organisations to the parents/ carers of young people with DMD in the UK, identified that short stature, obesity, and cushingoid features (including a puffy, rounded [moon] face) were of greatest concern to patients with DMD, whereas fractures, obesity, and delayed puberty were the side effects of most concern to parents. In August and September 2023, a survey of the community was conducted to record the experiences of steroid use, and vamorolone. There were 35 respondents, 5 of whom were adults with DMD who have been treated with steroids, 26 of whom were parents/carers of children who have been treated with steroids, and 4 of whom were the parent/carer of a child who had been on a vamorolone trial. 31 respondents reported they either took steroids every day, on alternate days, or ten days on and ten days off. 33 respondents completed the part of the survey asking about the benefits of steroids. They reported the following benefits: • Increase in energy (16 respondents) • Increase in ability to do physical activities and upper body use (19 respondents) • Delayed the loss of ambulation (19 respondents) • Reduced tiredness and increased the ability to concentrate and learn (11 respondents) • Helped with heart function (8 respondents) • Helped with breathing (5 respondents)

	One 23-year-old man reported he is still ambulant because of steroid treatment, and a 27-year-old reported he is not in a wheelchair 24/7 because of it. Another adult said that they struggled with weight and mood as a teenager, but the benefits outweigh the side effects now that they are older. 29 respondents replied 'yes' to the statement: "If you had the option, would you switch from steroid to vamorolone treatment?". No respondents replied 'no'.
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, which may subsequently result in changes to its availability in the UK: https://www.ema.europa.eu/en/news/ema-recommends-non-renewal-authorisation-duchenne-muscular-dystrophy-medicine-translarna Regardless of this, ataluren's mechanism of action is different to vamorolone's, and ataluren is only suitable for those patients with a nonsense mutation (which is approximately 10% of the DMD population). While corticosteroids should be considered for all patients with DMD (as described in section 7), some patients cannot tolerate this treatment due to the severity of the side effects. These patients are forced to withdraw from all steroid treatment despite the clinical advantages. These patients would benefit from an alternative to corticosteroids.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In our 2023 survey, all 4 of the parents/carers of children who took part in a vamorolone trial reported their child had taken part in the trial for between two and four years. The 4 parent/carers of children on a vamorolone trial were asked what benefits they had observed, and reported the following: • Increase in energy (3 respondents) • Increase in ability to do physical activities and upper body use (4 respondents) • Delayed the loss of ambulation (3 respondents) • Reduced tiredness and increased the ability to concentrate and learn (2 respondents) • Helped ith heart function (1 respondent) • Helped with breathing (1 respondent)

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	In terms of side effects, one member of the group in section 9 identified a weakening of bones and inactive adrenal glands. In informal discussion with our community, anxiety, and stimulated appetite leading to weight gain, are two more common disadvantages of vamorolone.

Patient population

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.	As covered in section 8, there are some patients who for various reasons cannot tolerate steroids. These patients would particularly benefit from the technology, as there are currently no alternatives. In addition, taking steroids for more than a month can cause the adrenal glands of patients to stop producing their own steroids. If the patient is then not given steroids, this can lead to potentially fatal adrenal crisis. For this reason, some clinicians decide not to prescribe steroids for patients who live in circumstances where there is a risk of interruption to their steroid regime. These patients will benefit from the technology more than others too.

Equality

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. 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

13. Are there any other issues that you would like the committee to consider?	No.

Key messages

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 the symptoms of DMD. • One of the only treatments, commonly prescribed and off-label, are corticosteroids: these come with recognised negative side effects. • These side effects also mean some patients cannot take corticosteroids. • There are few, if any, alternatives to corticosteroids. There is a huge need for alternatives for patients. • Vamorolone treatment may provide the benefits of corticosteroids, with a reduction in side effects typically associated with corticosteroids, and could be that much needed alternative.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - **YES** or ~~NO~~

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vamorolone for treating inflammation associated with Duchenne muscular dystrophy [ID4024]

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Duchenne UK. Duchenne UK has compiled this submission in collaboration with Action Duchenne and 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.
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.] **If so, please state the name of the company, amount, and purpose of funding.**	Duchenne UK have not received funding from ReveraGen in the last 12 months, but do have an interest in the technology (detailed below). Duchenne UK have received funding from Santhera in the last 12 months (detailed below). We have not published a position on the technology or the comparator in the last 12 months, beyond sharing factual information with our community. **ReveraGen** Duchenne UK have an interest in the technology. Duchenne UK entered into a grant funding agreement with ReveraGen in 2014 for the phase 1 study of vamorolone [redacted]. Duchenne UK has subsequently received a milestone payment when the commercial rights of the technology were sold [redacted], and Duchenne UK will receive further milestone payments based on future net sales of the product. **Santhera** Santhera have contributed as a member of the Duchenne UK-led Project HERCULES, [redacted]. Santhera have also agreed to be one of the industry sponsors of Duchenne UK's New Horizon conference which will be held in March 2024, [redacted].

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We have no links with the tobacco industry.

5. How did you gather information about the experiences of patients and carers to include in your submission?	Duchenne UK collaborated with other DMD patient organisations Action Duchenne and Muscular Dystrophy UK in producing this submission. There are three main sources of information:
	• Project HERCULES, a Duchenne UK-led international collaboration to develop evidence and tools to support HTA for new products for DMD. In particular:
	  ○ 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
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	• A 2020 survey conducted in collaboration with Pathfinders UK, Alex's Wish, Action Duchenne, Duchenne Family Support Group and Muscular Dystrophy UK recording the experiences of DMD patients. This was in preparation for the eventually discontinued NICE idebenone appraisal (ID1092) [GID-TA10310].
	• A survey of our community in August and September 2023 specifically on steroids, which asked respondents if they had taken part in a vamorolone trial

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 live male births in the UK. Patients generally exhibit symptoms between one and three years of age. There is no newborn screening program 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. The diagnosis of DMD is devastating for a family and there is often very little psychological support for them to come to terms with the diagnosis. Caregivers often suffer with depression and anxiety after diagnosis and have prolonged absences from work. Because of the progressive nature of the disease, the depression and anxiety continue as muscle function is lost - both for patients and their caregivers. 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. 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 may have learning disabilities or neurological disorders such as autism or learning disabilities. These usually remain static and do not worsen as DMD progresses. 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

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	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] 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-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) Standard medical management of DMD requires consideration of the use of corticosteroids as well as respiratory, cardiac, orthopaedic, and rehabilitative interventions (see section 7). The potential for corticosteroids was published in 1989 in a randomized, 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. The Finding the Optimum Regimen for Duchenne muscular dystrophy (FOR DMD) study compared three ways of giving corticosteroids to boys with DMD to determine which of the three ways increased muscle strength the most, and which causes the fewest side effects. This study was published in 2022[3], and reported that treatment with daily prednisone or daily deflazacort, compared with intermittent prednisone alternating 10 days on and 10 days off, resulted in significant improvement over 3 years in a composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment; there was no significant difference between the 2 daily corticosteroid regimens. The findings support the use of a daily corticosteroid regimen over the intermittent prednisone regimen tested in the study as initial treatment for boys with DMD. Steroids also have severe and very detrimental side effects that hugely impact on quality of life. Experiences of these side effects are elaborated on in section 6, but include: • serious effects on bone health leading to excess fractures which can cause pain and speed up the loss of muscle function • extreme weight gain

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[3] Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular DystrophyA Randomized Clinical Trial, Guglieri et al, JAMA, Apr 2022

	• adrenal insufficiency and crisis (if not administered correctly) • stunted growth, which causes psychological pain • delayed puberty and associated psychological challenges • behavioural problems.
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. There is no approved treatment which treats the underlying causes of DMD. Project HERCULES commissioned a study to gather qualitative evidence from patients and their parents on the adverse impact of long-term, high-dose steroid use side effects in DMD.[5] This found five prominent themes reported by the focus group; • **Physical appearance.** Physical appearance was a topic of high concern to both patients and parents and impacted on other areas including mental health, usual activities, and ability to "fit-in" socially. Main concerns were weight gain, short stature, and cushingoid appearance, all contributing to patients looking younger than their peers, which often resulted in them being treated differently. • **Delayed puberty.** Corticosteroids taken long-term can delay puberty, leading to a multitude of physical and mental complications. Testosterone is prescribed by some clinicians to induce puberty but parents reported that it was a challenge to get this prescribed and that response in those receiving it was varied. Patients reported that delayed puberty made them feel self-conscious and socially-isolated. • **Adrenal Crisis.** Patients taking long-term, high-dose corticosteroids are unable to produce heightened levels of cortisol required during times of physiological stress risking adrenal crisis, a life-threatening situation. Parents found this a huge burden as often emergency services are not trained to recognise the symptoms. Furthermore, schools may not be able to administer the injection and, instead, have to wait for a paramedic to arrive, meaning parents felt a need to always be near-by in case their child was injured/ ill so that they could explain the risks and make sure that the appropriate care was provided. • **Mood and behaviour.** Some of the parents felt that after starting steroids their child's behaviour changed drastically, with one parent describing it as the biggest burden they had experienced as a caregiver. HCPs reported that this is highly variable however existing neurodevelopmental conditions may be a factor in how a

[4] Diagnosis and management of Duchenne muscular dystrophy, part 1, Birnkrant et al, Lancet Neurology, Mar 2018, https://pubmed.ncbi.nlm.nih.gov/29395989/

[5] The burden of long-term corticosteroid use in the treatment of Duchenne Muscular Dystrophy in the UK, Tolley et al, Value in Health, Dec 2022, https://www.valueinhealthjournal.com/article/S1098-3015(22)04283-8/fulltext

	child responds emotionally and behaviourally when starting corticosteroid treatment. Several patients reported suffering with anxiety and low mood, however it is very difficult to ascertain how much is attributable to their condition, and whether taking a steroid exacerbates this or not. Both families and HCPs said there is not enough specialist psychological support available. • **Bone density.** Long-term corticosteroid use can reduce bone density leading to an increased risk of bone fractures. Both patients and parents reported this as being of high concern as it was linked to increased risk of adrenal crisis and worries over not being able to walk again and becoming non-ambulatory sooner. The study reported that an online survey, circulated via patient organisations to the parents/ carers of young people with DMD in the UK, identified that short stature, obesity, and cushingoid features (including a puffy, rounded [moon] face) were of greatest concern to patients with DMD, whereas fractures, obesity, and delayed puberty were the side effects of most concern to parents. In August and September 2023, a survey of the community was conducted to record the experiences of steroid use, and vamorolone. There were 35 respondents, 5 of whom were adults with DMD who have been treated with steroids, 26 of whom were parents/carers of children who have been treated with steroids, and 4 of whom were the parent/carer of a child who had been on a vamorolone trial. 31 respondents reported they either took steroids every day, on alternate days, or ten days on and ten days off. 33 respondents completed the part of the survey asking about the benefits of steroids. They reported the following benefits: • Increase in energy (16 respondents) • Increase in ability to do physical activities and upper body use (19 respondents) • Delayed the loss of ambulation (19 respondents) • Reduced tiredness and increased the ability to concentrate and learn (11 respondents) • Helped with heart function (8 respondents) • Helped with breathing (5 respondents)

	One 23-year-old man reported he is still ambulant because of steroid treatment, and a 27-year-old reported he is not in a wheelchair 24/7 because of it. Another adult said that they struggled with weight and mood as a teenager, but the benefits outweigh the side effects now that they are older. 29 respondents replied 'yes' to the statement: "If you had the option, would you switch from steroid to vamorolone treatment?". No respondents replied 'no'.
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, which may subsequently result in changes to its availability in the UK: https://www.ema.europa.eu/en/news/ema-recommends-non-renewal-authorisation-duchenne-muscular-dystrophy-medicine-translarna Regardless of this, ataluren's mechanism of action is different to vamorolone's, and ataluren is only suitable for those patients with a nonsense mutation (which is approximately 10% of the DMD population). While corticosteroids should be considered for all patients with DMD (as described in section 7), some patients cannot tolerate this treatment due to the severity of the side effects. These patients are forced to withdraw from all steroid treatment despite the clinical advantages. These patients would benefit from an alternative to corticosteroids.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In our 2023 survey, all 4 of the parents/carers of children who took part in a vamorolone trial reported their child had taken part in the trial for between two and four years. The 4 parent/carers of children on a vamorolone trial were asked what benefits they had observed, and reported the following: • Increase in energy (3 respondents) • Increase in ability to do physical activities and upper body use (4 respondents) • Delayed the loss of ambulation (3 respondents) • Reduced tiredness and increased the ability to concentrate and learn (2 respondents) • Helped ith heart function (1 respondent) • Helped with breathing (1 respondent)

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	In terms of side effects, one member of the group in section 9 identified a weakening of bones and inactive adrenal glands. In informal discussion with our community, anxiety, and stimulated appetite leading to weight gain, are two more common disadvantages of vamorolone.

Patient population

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.	As covered in section 8, there are some patients who for various reasons cannot tolerate steroids. These patients would particularly benefit from the technology, as there are currently no alternatives. In addition, taking steroids for more than a month can cause the adrenal glands of patients to stop producing their own steroids. If the patient is then not given steroids, this can lead to potentially fatal adrenal crisis. For this reason, some clinicians decide not to prescribe steroids for patients who live in circumstances where there is a risk of interruption to their steroid regime. These patients will benefit from the technology more than others too.

Equality

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. 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

13. Are there any other issues that you would like the committee to consider?	No.

Key messages

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 the symptoms of DMD. • One of the only treatments, commonly prescribed and off-label, are corticosteroids: these come with recognised negative side effects. • These side effects also mean some patients cannot take corticosteroids. • There are few, if any, alternatives to corticosteroids. There is a huge need for alternatives for patients. • Vamorolone treatment may provide the benefits of corticosteroids, with a reduction in side effects typically associated with corticosteroids, and could be that much needed alternative.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vamorolone for treating inflammation associated with Duchenne muscular dystrophy [ID4024]

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

1.Your name	[redacted]
2. Name of organisation	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?	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.
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.] **If so, please state the name of the company, amount, and purpose of funding.**	None.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.

5. How did you gather information about the experiences of patients and carers to include in your submission?	Muscular Dystrophy UK collaborated with other DMD patient organisations (Action Duchenne and Duchenne UK) in producing this submission. There are three main sources of information:
	• Project HERCULES, a Duchenne UK-led international collaboration to develop evidence and tools to support HTA for new products for DMD. In particular:
	  ○ 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
	  ○ The burden of long-term corticosteroid use in the treatment of Duchenne Muscular Dystrophy in the UK, Tolley et al, Value in Health, Dec 2022, https://www.valueinhealthjournal.com/article/S1098-3015(22)04283-8/fulltext
	  ○ 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
	• A 2020 survey conducted in collaboration with Pathfinders UK, Alex's Wish, Action Duchenne, Duchenne Family Support Group and Muscular Dystrophy UK recording the experiences of DMD patients. This was in preparation for the eventually discontinued NICE idebenone appraisal (ID1092) [GID-TA10310].
	• A survey of our community in August and September 2023 specifically on steroids, which asked respondents if they had taken part in a vamorolone trial

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 live male births in the UK. Patients generally exhibit symptoms between one and three years of age. There is no newborn screening program 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. The diagnosis of DMD is devastating for a family and there is often very little psychological support for them to come to terms with the diagnosis. Caregivers often suffer with depression and anxiety after diagnosis and have prolonged absences from work. Because of the progressive nature of the disease, the depression and anxiety continue as muscle function is lost - both for patients and their caregivers. 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. 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 may have learning disabilities or neurological disorders such as autism or learning disabilities. These usually remain static and do not worsen as DMD progresses. 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

[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

	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] 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-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) Standard medical management of DMD requires consideration of the use of corticosteroids as well as respiratory, cardiac, orthopaedic, and rehabilitative interventions (see section 7). The potential for corticosteroids was published in 1989 in a randomized, 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. The Finding the Optimum Regimen for Duchenne muscular dystrophy (FOR DMD) study compared three ways of giving corticosteroids to boys with DMD to determine which of the three ways increased muscle strength the most, and which causes the fewest side effects. This study was published in 2022[3], and reported that treatment with daily prednisone or daily deflazacort, compared with intermittent prednisone alternating 10 days on and 10 days off, resulted in significant improvement over 3 years in a composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment; there was no significant difference between the 2 daily corticosteroid regimens. The findings support the use of a daily corticosteroid regimen over the intermittent prednisone regimen tested in the study as initial treatment for boys with DMD. Steroids also have severe and very detrimental side effects that hugely impact on quality of life. Experiences of these side effects are elaborated on in section 6, but include: • serious effects on bone health leading to excess fractures which can cause pain and speed up the loss of muscle function • extreme weight gain

[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

[3] Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular DystrophyA Randomized Clinical Trial, Guglieri et al, JAMA, Apr 2022

	• adrenal insufficiency and crisis (if not administered correctly) • stunted growth, which causes psychological pain • delayed puberty and associated psychological challenges • behavioural problems.
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. There is no approved treatment which treats the underlying causes of DMD. Project HERCULES commissioned a study to gather qualitative evidence from patients and their parents on the adverse impact of long-term, high-dose steroid use side effects in DMD.[5] This found five prominent themes reported by the focus group; • **Physical appearance.** Physical appearance was a topic of high concern to both patients and parents and impacted on other areas including mental health, usual activities, and ability to "fit-in" socially. Main concerns were weight gain, short stature, and cushingoid appearance, all contributing to patients looking younger than their peers, which often resulted in them being treated differently. • **Delayed puberty.** Corticosteroids taken long-term can delay puberty, leading to a multitude of physical and mental complications. Testosterone is prescribed by some clinicians to induce puberty but parents reported that it was a challenge to get this prescribed and that response in those receiving it was varied. Patients reported that delayed puberty made them feel self-conscious and socially-isolated. • **Adrenal Crisis.** Patients taking long-term, high-dose corticosteroids are unable to produce heightened levels of cortisol required during times of physiological stress risking adrenal crisis, a life-threatening situation. Parents found this a huge burden as often emergency services are not trained to recognise the symptoms. Furthermore, schools may not be able to administer the injection and, instead, have to wait for a paramedic to arrive, meaning parents felt a need to always be near-by in case their child was injured/ ill so that they could explain the risks and make sure that the appropriate care was provided. • **Mood and behaviour.** Some of the parents felt that after starting steroids their child's behaviour changed drastically, with one parent describing it as the biggest burden they had experienced as a caregiver. HCPs reported that this is highly variable however existing neurodevelopmental conditions may be a factor in how a

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[5] The burden of long-term corticosteroid use in the treatment of Duchenne Muscular Dystrophy in the UK, Tolley et al, Value in Health, Dec 2022, https://www.valueinhealthjournal.com/article/S1098-3015(22)04283-8/fulltext

	child responds emotionally and behaviourally when starting corticosteroid treatment. Several patients reported suffering with anxiety and low mood, however it is very difficult to ascertain how much is attributable to their condition, and whether taking a steroid exacerbates this or not. Both families and HCPs said there is not enough specialist psychological support available. • **Bone density.** Long-term corticosteroid use can reduce bone density leading to an increased risk of bone fractures. Both patients and parents reported this as being of high concern as it was linked to increased risk of adrenal crisis and worries over not being able to walk again and becoming non-ambulatory sooner. The study reported that an online survey, circulated via patient organisations to the parents/ carers of young people with DMD in the UK, identified that short stature, obesity, and cushingoid features (including a puffy, rounded [moon] face) were of greatest concern to patients with DMD, whereas fractures, obesity, and delayed puberty were the side effects of most concern to parents. In August and September 2023, a survey of the community was conducted to record the experiences of steroid use, and vamorolone. There were 35 respondents, 5 of whom were adults with DMD who have been treated with steroids, 26 of whom were parents/carers of children who have been treated with steroids, and 4 of whom were the parent/carer of a child who had been on a vamorolone trial. 31 respondents reported they either took steroids every day, on alternate days, or ten days on and ten days off. 33 respondents completed the part of the survey asking about the benefits of steroids. They reported the following benefits: • Increase in energy (16 respondents) • Increase in ability to do physical activities and upper body use (19 respondents) • Delayed the loss of ambulation (19 respondents) • Reduced tiredness and increased the ability to concentrate and learn (11 respondents) • Helped with heart function (8 respondents) • Helped with breathing (5 respondents)

	One 23-year-old man reported he is still ambulant because of steroid treatment, and a 27-year-old reported he is not in a wheelchair 24/7 because of it. Another adult said that they struggled with weight and mood as a teenager, but the benefits outweigh the side effects now that they are older. 29 respondents replied 'yes' to the statement: "If you had the option, would you switch from steroid to vamorolone treatment?". No respondents replied 'no'.
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, which may subsequently result in changes to its availability in the UK: https://www.ema.europa.eu/en/news/ema-recommends-non-renewal-authorisation-duchenne-muscular-dystrophy-medicine-translarna Regardless of this, ataluren's mechanism of action is different to vamorolone's, and ataluren is only suitable for those patients with a nonsense mutation (which is approximately 10% of the DMD population). While corticosteroids should be considered for all patients with DMD (as described in section 7), some patients cannot tolerate this treatment due to the severity of the side effects. These patients are forced to withdraw from all steroid treatment despite the clinical advantages. These patients would benefit from an alternative to corticosteroids.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In our 2023 survey, all 4 of the parents/carers of children who took part in a vamorolone trial reported their child had taken part in the trial for between two and four years. The 4 parent/carers of children on a vamorolone trial were asked what benefits they had observed, and reported the following: • Increase in energy (3 respondents) • Increase in ability to do physical activities and upper body use (4 respondents) • Delayed the loss of ambulation (3 respondents) • Reduced tiredness and increased the ability to concentrate and learn (2 respondents) • Helped ith heart function (1 respondent) • Helped with breathing (1 respondent)

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	In terms of side effects, one member of the group in section 9 identified a weakening of bones and inactive adrenal glands. In informal discussion with our community, anxiety, and stimulated appetite leading to weight gain, are two more common disadvantages of vamorolone.

Patient population

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.	As covered in section 8, there are some patients who for various reasons cannot tolerate steroids. These patients would particularly benefit from the technology, as there are currently no alternatives. In addition, taking steroids for more than a month can cause the adrenal glands of patients to stop producing their own steroids. If the patient is then not given steroids, this can lead to potentially fatal adrenal crisis. For this reason, some clinicians decide not to prescribe steroids for patients who live in circumstances where there is a risk of interruption to their steroid regime. These patients will benefit from the technology more than others too.

Equality

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. 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

13. Are there any other issues that you would like the committee to consider?	No.

Key messages

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 the symptoms of DMD. • One of the only treatments, commonly prescribed and off-label, are corticosteroids: these come with recognised negative side effects. • These side effects also mean some patients cannot take corticosteroids. • There are few, if any, alternatives to corticosteroids. There is a huge need for alternatives for patients. • Vamorolone treatment may provide the benefits of corticosteroids, with a reduction in side effects typically associated with corticosteroids, and could be that much needed alternative.

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

Vamorolone for treating inflammation associated with Duchenne muscular dystrophy [ID4024]

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

1. Your name	[redacted]
2. Name of organisation	Associate of British Neurologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	A specialist in the clinical evidence bases for this condition or technology? Yes
5a. Brief description of the organisation (including who funds it).	ABN is an independent organisation representing UK neurologists helping to promote excellent standards of care and champion high-quality education and world-class research in neurology. It is funded by its members who pay membership fees.
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.] **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

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.)	Vamorolone is a dissociative synthetic steroid. The treatment aims to: 1.Maintain the muscle strength and function. 2.To improve the height velocity in children with DMD. 3.Possible cardioprotective effect, as shown in pre-clinical trials. 4.Bone protection
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.)	Delayed “loss of ambulation” Preservation or improvement of cardiac, respiratory, upper arm function. Lesser medication related adverse effects.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Currently patients have limited treatment options, that effectively delay or reverse disease progression, and the high cost of marketed therapies. Patients currently use steroids in the form of prednisolone or similar agents which are associated with significant side effects and therefore treatment withdrawal despite its known advantages. There is therefore a proportion of patients who are unable to tolerate steroid treatment that need other alternatives.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	1. Glucocorticoids (Prednisolone and Deflazacort, using different regimens) 2. Symptomatic treatment 3. Genetic therapies: Mutation specific disease modifying treatments

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes-International and National Standards of Care: 1. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management **https://doi.org/10.1016/S1474-4422(18)30024-3** 2. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management; Published in 2018 doi: 10.1016/S1474-4422(18)30025-5 3. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan https://doi.org/10.1016/S1474-4422(18)30026-7 4. Adult North Star Network (ANSN): Consensus Guideline For The Standard Of Care Of Adults With Duchenne Muscular Dystrophy; DOI: 10.3233/JND-200609
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	Yes- in Specialised Neuromuscular Centres. The standards of care are not a mandated and therefore there is significant variability in delivery across the different centres.

experience is from outside England.)	
9c. What impact would the technology have on the current pathway of care?	None
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	N/A
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Clinics
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	As opposed to standard corticosteroids, vamolorone — a first-in-class steroidal product — has a mechanism of action that "dissociates efficacy from safety," causing fewer and less-severe side effects without compromising its anti-inflammatory properties. We would expect it to deliver similar benefits as current treatment but with better tolerability and compliance.
11a. Do you expect the technology to increase	Further research is required especially related to its cardioprotective benefits as this is where it may have potential to alter length of life.

length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. 1.Possibly by decreasing bone morbidities. 2. Decreasing the adrenal suppression and insulin resistance 3. Preventing growth delay 4. Increasing compliance and therefore being more likely to benefit patients
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No difference in efficacy between groups.

The use of the technology

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	The medication is delivered orally which is the same as current medication. The monitoring prerequisites are routine blood tests and radiologic (bone) investigations which are the same as currently used for standard corticosteroids.

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?	Likely to be used primarily in patients who could not tolerate corticosteroids due to side effects or those with poor compliance.
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?	No
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?	Possibly - it might improve some aspects of quality of life, related to fewer adverse effects and better compliance with better treatment and hence better outcomes in those scenarios
16a. Is the technology a 'step-change' in the management of the condition?	No

16b. Does the use of the technology address any particular unmet need of the patient population?	Partially in patients who cannot tolerate steroids. There is also evidence in animal models that Vamorolone has a cardioprotective effect. This has not been investigated in humans yet but if shown to be the case may improve outcomes.
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?	All are treatable as per current standards of care guidelines.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Timed function tests and NorthStar Ambulatory Assessment. Both measured in the trial and compared with natural history data of DMD.
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?	The clinical trial was conducted in heterogenous, paediatric group with a narrow age, using different dose regimens. Further data are needed, to assess the long-term adverse effects.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	N/A

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Valmorolone causes fewer and less-severe side effects without compromising its anti-inflammatory properties. It has a similar efficacy on maintaining the muscle function as the current standard of care treatment options. • Given its improved side effect profile it is better tolerated and associated with better compliance in patients with DMD. This is turn potentially may improve long term outcomes. • Might have a cardioprotective protective effects, as it acts as an antagonist to mineralocorticoid receptors, as shown in preclinical trials but further data is needed. • The trial was conducted in a heterogenous paediatric group and included narrow age range. Further research and clinical experience are necessary.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vamorolone for treating inflammation associated with Duchenne muscular dystrophy [ID4024]

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

1. Your name	[redacted]
2. Name of organisation	BSPED (British Society for Paediatric Endocrinology & Diabetes) and BPABG (British Paediatric And Adolescent Bone Group)
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 A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	**BSPED** - professional society which aims to improve the care of children and young people with endocrine disorders or diabetes mellitus. Funded via membership fees and corporate support **BPABG** - clinicians interested in paediatric bone disease. Some funding from educational events
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.] **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,	no

the tobacco industry?	

The aim of treatment for this condition

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.)	
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.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	High dose steroids - either Prednisolone or Vamorolone

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	
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.)	DMD standards of care published in Lancet Neurology 2018
9c. What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example,	

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
11a. Do you expect the technology to increase length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	

The use of the technology

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.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
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?	
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?	
16a. Is the technology a 'step-change' in the	

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	
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18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Steroids (glucocorticoids) used in high doses have significant side effects (weight gain, osteoporosis, adrenal suppression, poor growth, delayed puberty) • The side effects of Vamorolone are not well described • The side effects will need to be monitored and guidance on monitoring and treatment provided. • •

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

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Patient expert statement

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Your response should not be longer than 15 pages.

The deadline for your response is **5:00pm** on **31 January 2024.** 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, 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 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with Duchenne muscular dystrophy

Table 1 About you, Duchenne muscular dystrophy, current treatments and equality

1. Your name	Robert Burley
2. Are you (please tick all that apply)	☐ A patient with Duchenne muscular dystrophy? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Duchenne muscular dystrophy? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Muscular Dystrophy 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) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing this statement
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	Muscular Dystrophy UK is the leading charity for over 60 muscle wasting and weakening conditions. For over 60 years, we've been building our community of individuals living with muscle wasting or weakening conditions, families and carers, scientists, health professionals, supporters, volunteers, and donors. Making advances that would have been unthinkable just ten years ago. We connect our community of more than 110,000 people, and all the people around them. So they can get the healthcare, support and treatments they need to feel good, mentally and physically. Through advice and support, research, campaigning, and fundraising. I lead the charity's information, advocacy and support service which involves supporting individuals and families affected by Duchenne muscular dystrophy. I also lead our policy and campaigns activity, which includes our work around access to treatments. I am in regular dialogue with the Duchenne community and am responsible for ensuring that the views and experience of people with the condition is at the heart of our work. In order to help with this response, Muscular Dystrophy UK surveyed 73 people affected by Duchenne muscular dystrophy between 7-12 February 2024, with questions that aligned with the questions in this form. Three respondents have Duchenne muscular dystrophy; 64 are parents of a child with Duchenne muscular dystrophy; two are carers; three are grandparents; and one is a consultant. ☒ I have completed part 2 of the statement. There was no expert engagement teleconference.
6. What is your experience of living with Duchenne muscular dystrophy? **If you are a carer (for someone with Duchenne muscular dystrophy) please share your experience of caring for them**	The joint appraisal submission by Muscular Dystrophy UK, Action Duchenne and Duchenne UK provides a summary of the experience of living with Duchenne muscular dystrophy and of caring for someone with Duchenne muscular dystrophy.
7a. What do you think of the current treatments and care available for	We asked this question directly in our survey and 72 people responded. 41 people (57%) said that their experience of current treatments and care was 'poor' or 'very poor'. 16 people (22%) said that their experience of current treatments and care was 'good' or 'very good'. 13 people (18%) said that their experience of current treatment and care was 'neither good nor poor'.

Duchenne muscular dystrophy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Survey respondents reported that prolonged ambulation and greater mobility were a positive gained form current corticosteroid treatment. *"On his current steroid treatment, our son has been able to maintain the ability to walk, because of relatively good muscle function."* The lack of any real alternative to corticosteroid treatment was widely noted. *"The care and support we've received has been excellent but the treatments available are extremely limited and almost non-existent. Currently conventional steroids such as Prednisolone are the only option".* *"I cannot fault our physiotherapy treatment and other professionals involved but the actual lack of treatment for Duchenne is poor".* *"The only treatment there is steroids. We were really given no choice but to put him on them".* *"Gold standard is not good enough with generalised steroids".* *"Limited choice mainly down to two steroids both with distinctive disadvantages".* *"The understanding and care is great, the push for steroids though makes us feel pressured though without it being possible to weigh the positives and negatives".* *"The care is excellent but the options available to actually help them is pretty much non-existent".* 100% of survey respondents were in favour of additional treatment options being made available for Duchenne muscular dystrophy. The specific disadvantages of existing corticosteroid treatments are explored further in the next question.

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	The disadvantages of corticosteroid treatment currently available through the NHS are well documented and were reflected in our survey findings. 100% of respondents reported disadvantages, with the five main ones being weight gain (and corresponding self-esteem issues); negative behaviour changes; stunted growth/growth restriction; reduced bone density; and delayed puberty. *"My son gained 3 stone in 1 year, and still lost the ability to walk".* *"We are aware of issues with temperament and have experienced occasional outbursts, though not as bad as have been reported with some other young corticosteroid users and are keeping an eye on development through puberty as that can be delayed".* *"Massive side effects in my son - behavioural changes, weight changes, did not start puberty himself required hormone treatment, taste changes, brittle or weak bones requiring calcium treatment, Cushing's syndrome, body fat on neck, red and puffy face, increase in body hair, severe acne. Had to have chicken pox vaccine as was not immune at start of taking steroids, start of glaucoma, anxiety, osteoporosis, irritability".* *"My 7-year-old son has had 4 vertebral fractures".* *"Stunted growth is also an issue & has a negative impact on emotional & mental health."* The wider impact of the disadvantages of corticosteroid treatment were noted by survey respondents e.g. impact on education. *"Vomiting as school are quick to send home even if they know he's on medication."* The disadvantages of corticosteroid treatment can be experienced so acutely that some survey respondents questioned whether they in fact outweigh the treatment advantages they bring. *"I find that the potential for my child to develop adrenal crisis; if seriously unwell, is something that not only has brought an element of anxiety and fear to caring for my child, but it has also led to an*

	increased level of not wanting him to be on steroids. I find myself constantly feeling as though he'd be a different child off them, mood wise too." *"The side effects of the treatment almost outweigh the benefits."*
9a. If there are advantages of Vamorolone 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? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Vamorolone 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**	Given the reported disadvantages of corticosteroid treatment, it is not surprising that the main advantage of vamorolone was given as the absence/significant reduction in these. One parent was able to share the compared experience of their two sons, both of whom have Duchenne muscular dystrophy – with one receiving vamorolone and one receiving a corticosteroid treatment. *"I have one son that gets current steroid treatment, and the other gets vamorolone (both with DMD). The vamorolone didn't delay growth at all for him, no round face, no overweight. Also seem to be able to walk until later age before a need for permanent wheelchair use is being raised. As a mother, I see a great advantage of vamorolone over prednisone when comparing the two treatments (as appears in our family)."* Ultimately, survey respondents reported that the reduced side-effects of vamorolone translated into better quality of life; both for individuals receiving the treatment and for their families. *"They have the potential to grow in line with other boys their age. They have the potential to stay on their feet for longer. This has a ripple effect for everyone's quality of life including siblings & parents. Parents can stay in work for longer, offering better financial stability. We can enjoy more family holidays; boys can gain more independence & have a greater social life".* *"Increased quality of life. Increased self-worth. Ability to form more stable interpersonal relationships."* *"Vamorolone would remove some of the side effects of current steroids. For our son this would improve his self-confidence improving his independence to go out, to work and improve his self-care. As a family, if our son is more independent then we are able to continue working and spend time with our other son".*

	"As a high-school age child dealing with DMD, both the social and learning aspects can be heavily compromised which will have effects now and repercussions in later life. The reduced side-effects could make a significant difference in terms of self-image, confidence and independence, all feeding into quality of life". One survey respondent noted a practical advantage of vamorolone over current corticosteroid treatments. *"Vamorolone comes in a liquid formulation, which can be advantageous for some (usually younger) patients".*
10. If there are disadvantages of Vamorolone over current treatments on the NHS please describe these. For example, are there any risks with Vamorolone? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As outlined in the joint appraisal submission by Muscular Dystrophy UK, Action Duchenne and Duchenne UK, one person with experience of vamorolone has shared their experience of a weakening of bones and inactive adrenal glands. Informal discussions with the community have referenced anxiety and stimulated appetite leading to weight gain as two possible disadvantages of vamorolone.
11. Are there any groups of patients who might benefit more from Vamorolone or any who may benefit less? If so, please describe them and explain why	Intentionally blank.
12. What influences patient and caregiver preferences when considering different treatments for DMD?	Survey respondents listed five main factors that influence their consideration of different treatments. These are its efficacy/whether it will delay the progression of Duchenne; whether it will improve quality of life; the likely side effects (including weight gain, bone weakness and behaviour); whether it will help maintain mobility; and its safety.

13. What are patients views on vamorolone potentially having reduced efficacy compared to other treatments in terms of muscle function outcomes but potentially an improved safety profile (for example reduced stunted growth and behavioural issues)**?**	Our current understanding based on discussions with clinical experts is that whilst there is an absence of longitudinal data, the evidence available so far does not seem to suggest a significant difference in efficacy between vamorolone and traditional corticosteroids over the first 30 months of treatment. I understand from correspondence with the NICE team that the EAG has a different interpretation of the data available, and I look forward to this being explored at the committee meeting where the expertise of the EAG, the company and the clinical experts will be extremely valuable. In our survey we relayed this question as worded i.e. without expressing an opinion as to whether or not we agreed with the inference. 10 of the 56 survey respondents who answered this question (18%) challenged the assumption on efficacy; four of the 56 survey respondents who answered this question (7%) expressed concern about the implications of this interpretation on their own understanding of the situation; and 31 of the 56 survey respondents who answered this question (55%) approached it at 'face value' and were broadly of the view that pending a detailed assessment tailored to individual circumstances, vamorolone would possibly still be a preferred treatment option. Comments from the 18% of people who challenged the assumption on efficacy included: *"I don't agree with the statement as research has shown that vamorolone was comparable to prednisolone in terms of muscle function outcomes".* *"The study information I have read indicates a similar efficacy to current offerings but with a much more favourable safety profile".* *"This is a leading question... Not seen any evidence to say that efficacy is reduced with vamorolone, I believe there is much of a muchness. This implies that there is a big difference. I would like to understand what the efficacy difference is between the drugs. I would expect the clinician to talk me through this before we make a decision to swap".* *"Not aware that this has been expressly demonstrated in trials so perhaps more of a what if question, and in that context has no relevance at this time".* *"Vamorolone provides same efficacy as other treatments with reduced side effects".*

	"Insufficient information to form a credible answer". *"This is minimal, the efficacy is clearly considerably higher than current steroids".* *"I feel that vamorolone appears not to reduce efficacy as my son has not displayed much of a decline yet".* *"There's never been enough evidence of the efficacy of corticosteroids but there's a lot of evidence of how awful the side effects of them are, so would prefer vamorolone even in this case".* *"It doesn't have reduced efficacy at 6mg/kg dose - this is an incorrect/biased statement".* The four people who expressed concern about the implications of this interpretation shard that: *"Didn't know that. Hard to make a choice when nothing is perfect".* *"I'm not sure quite how I feel about this yet".* *"I would want to know more about this before deciding to change from corticosteroids".* *"It worries me".* An important theme in the 55% of those responses that took it on 'face value' was the importance of informed decision making based on individual circumstances and in partnership with a clinician familiar with the patient making the decision. *"This is something that is not great as muscle function is the one we want to be the best but overall helping more with the other issues could help them lead a happier life. I feel that it will be a very individual decision between parents, child and consultant on if it would be beneficial for that child".*

	"We are conscious that every situation is different, and that some corticosteroid users experience side effects so pronounced that their accepted threshold for efficacy would understandably be lower than ours, if in those instances the side effects are causing a serious detriment to the quality of life of the recipient and those around them". It was also noted that an improved safety profile could potentially result in people being able to tolerate remaining on treatment for a longer period. *"It might result in longer term use. My son decided to stop at age 15 due to side effects- he hated how it made him look and feel. He may still be taking them at 20."* Many of these respondents suggested that the negative side effects of existing corticosteroid treatments were so acute that the benefit of these being reduced might outweigh an assumed reduced efficacy. *"As the boys deteriorate anyway we start to see less benefit and only increased side effects risk. if a treatment has reduced efficacy but also reduce risk as parents we will be happier to carry on treatment longer rather than curtail treatment".* *"I will take an improved safety profile over improved muscle function any day of the week".* *"An improved safety profile is of the utmost importance to me. My son's growth and behavioural issues have been huge sources of concern; I'd take improvement in safety profile over muscle function outcomes, especially if unwanted problematic side effects were reduced/eliminated".* *"It would depend how much worse the efficacy was. if it was marginal or a small difference, vamorolone would still be my preferred treatment".* *"I think I would rather have that than all the side effects from steroids we are now dealing with".*

	"In our instance, a slightly reduced efficacy but better safety profile would be an acceptable balance; if the efficacy was significantly worse than corticosteroid equivalents then it would tip the balance and become an unviable option".
12. Are there any potential equality issues that should be taken into account when considering Duchenne muscular dystrophy and Vamorolone? Please explain if you think any groups of people with this condition are particularly disadvantage 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 More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Intentionally blank.
13. Are there any other issues that you would like the committee to consider?	The anguish experienced by carers when faced with decisions about existing corticosteroid treatment and the huge impact of watching a child experience their negative side effects cannot be understated.

	"[On vamorolone] we would no longer feel as guilty about giving steroids to our sons which ultimately causes long term pain for short term gains. It's a massive decision to put boys on steroids. My husband and I argued for weeks over it. It's an emotive decision which requires a lot of thought. You make the decision out of love but ultimately, it's always the wrong decision whichever way you look at it as you feel a constant guilt that you are giving something to your son that is harming him. Vamorolone eases that pressure significantly because one of the most critical side effects is now not much of an issue". *"Our 7-year son was diagnosed with DMD in December 2022. Placing him on Prednisolone steroid treatment was an extremely challenging and difficult decision to have to make. But there was no alternative given the natural history and course of the disease. Every morning he willingly takes his steroid. I know that they are helping but I feel like I'm poisoning him and impacting his quality of life in many other ways given the severe side effects. Our mental health is impacted not only by Duchenne muscular dystrophy but by the very steroid treatment he is receiving. We both have had time off work, do not sleep well, and struggle day-to-day."* *"[On vamorolone] I wouldn't feel so guilty for putting him on steroids and causing all the side effects. I question myself all the time whether we have done the right thing."* At the end of our survey we invited respondents to provide any final thoughts. *"Following my son taking Vamorolone - strongly recommend it's made available to all".* *"The sheer hopelessness is mentally and physically debilitating on not just the boys but the family as a whole. The cost of this cannot be ignored as the costs to the economy in stress related illness is significant with parents having to frequently take time off and absences from work. A new treatment that offers some hope for an extended lifespan for our boys is significant".* *"There have been so few positives until vamorolone came along and offers the chance of something of a normal childhood which would be incredible".*

	"This is a life changing disease for patients and all family members. Vamorolone is a step forward and represents a lesser evil to traditional steroids which are horrible drugs with respect to side effects". *"Steroids are poor treatments and vamorolone is a massive shift in right direction. There are little available treatments for such a life limiting disease so this is step in right direction".*

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Duchenne muscular dystrophy is a devastating condition with extremely limited treatment options and no cure.
- There is an urgent need for a wider range of treatment options and a significant degree of unmet need.
- Existing corticosteroid treatments can come with such acute side-effects that parents question their benefit and often feel that the negative impact on the lives of their children and wider family outweigh the benefits.
- Retaining ambulation and muscle function is a key consideration when families make decisions about treatment options and condition management; but so is quality of life and overall wellbeing.
- There is a strong view from within the Duchenne community that vamorolone is a potential 'game changer' and that access to it has the potential to bring significant improvements to the lived experience of an individual and family affected by Duchenne muscular dystrophy.

Thank you for your time.

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Single Technology Appraisal

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The deadline for your response is **5:00pm** on **31 January 2024.** 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, 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 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with Duchenne muscular dystrophy

Table 1 About you, Duchenne muscular dystrophy, current treatments and equality

1. Your name	Mandy Roe
2. Are you (please tick all that apply)	☐ A patient with Duchenne muscular dystrophy? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with Duchenne muscular dystrophy? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
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) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing this statement
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement an there was no expert engagement teleconference

	☐ I have not completed part 2 of the statement
6. What is your experience of living with Duchenne muscular dystrophy? **If you are a carer (for someone with Duchenne muscular dystrophy) please share your experience of caring for them**	My child was diagnosed at the age of 3. This changed my whole life in every single aspect. I went from being a mother with three healthy children who I would take to school, clubs, playdates, parties and on carefree family holidays to a mum full of grief, hospital appointments, constant other appointments, and more contact with medical teams than I could ever have thought possible. Life changed for us as a family. I became a mum of three to also being a full-time carer, trying to hold myself together whilst going through the worst heartbreak I could ever imagine possible. Life as I knew it would never be the same again. There are so many aspects to being a carer for a child with this condition it's hard to try and summaries it to people on paper. When the child starts to lose their abilities, it starts off with endless appointments with new equipment being added to help maintain their muscles, posture, heart, lungs and much more. As they grow older you become not only their carer but their voice with school and with various medical professionals. The older my son has gotten each year the care that is needed has increased month by month. The worries have changed. You don't lose the worries they just change to new ones. When he was younger the main worry was him falling. There were so many times he would trip, drop or fall and end up with cuts all over his legs, hands and face. School has always been incredibly hard for my son as he could see he was not able

	to do things his peers could do. Getting the care he needs in school is, and always has been, a struggle and a fight. As he has gotten older, the care he needs has become much more physically intense which has led to me having to do a lot more physically. Physio has become hard. Carrying him, and transferring him from place to place. I would do anything for my son and more but at 39 my back is in such a bad way the only thing the specialists say I could do to relieve the pain would be to go for an operation which would mean 3/6 months off my feet. Being my son's full time carer, this could never be an option. I am a carer from morning to night, responsible for medication, washing, brushing his teeth, dressing and undressing, cutting up food, getting him in his chair and out of his chair, helping him every time he needs the toilet, and attending appointments most weeks. He has a physio routine at home which I do He has a standing frame to help keep his spine straight. Being a full-time carer is extremely emotionally difficult and physically hard on my body. Being a carer is lying awake at night worrying about the next scan; the next appointment. Worrying what is next on the cards of this journey. It's battling constantly for the care your child needs or adjustments they need. It's having to plan in detail every trip out, every restaurant we visit to make sure it's accessible, not being able to visit family and friends at home because your son's chair can't get through the door, meticulously planning your holidays from transfer on to the plane, transfers to the hotel, accessible hotels and trips that you can enjoy and have a much needed break and family time away from the constant battles and heart ache. So to summarise - being a career for someone with this condition is hard, a constant heart break, physically draining and somewhere your mind can never turn

	off but you battle through for someone who is not only your son but a piece of you that you would move heaven and earth for.
7a. What do you think of the current treatments and care available for Duchenne muscular dystrophy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The current treatments for Duchenne in my opinion are very intense on the boys. As set out in question 9, my son had the experience of benefitting from vamorolone through a trail we started in 2017 which means he was on the drug for over 6 years and then having to come off it and moving to currently available NHS treatments, meaning he has had an acute experience of the side effects of the currently available treatments in comparison to vamorolone. My son moved on to a steroid that is available on the NHS in March 2023. We were aware of some possible side effects but had to move on to them to be able to access another medical trial. Since we have moved on to the NHS recommended treatment steroid it's been a terrible decline for my son and lots of negative side effects. My son was walking independently when we moved on to the NHS steroid and within days the falls became much more frequent and by June 2023 he was not able to walk a single step. He also experienced rapid weight gain. We have done everything to help control the weight gain including exercises in the hot tub, swimming three times a week and the strictest diet we could possibly have tried; yet the gain continued to pile on at an alarming rate and nothing we could do was able to slow it down. For the first time since diagnosis my son has become so unhappy, he is heartbroken at the massive weight gain. He openly says that he lost the ability to walk since he went on to these steroids. He cries over the fact his face is so swollen

	– it is red and blotchy and for us as a family there is no debating that the NHS steroids have caused this and left my son with even more heart break. I've spoken to several parents about the use of the steroids that are used by NHS. We all share our thoughts and views. We are like a family we didn't choose; but we understand each other more than people we have known our whole lives so discussions like this are normal. I've not come across one parent of a child with Duchenne who like the steroids that are available or are happy to start them because of the hard and devastating side effects; but we have no choice but to try because so far they are the only things that could prolong our sons' time on this earth. In my opinion the treatments available cause devastating side effects for boys - weak bones; weight gain; emotional outbursts; 'moon face'; and delayed puberty. These treatments are only the best of a bad choice and there is a massive lack of any other of option for any of us.
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	Side effects in my experience include weight gain that is uncontrollable no matter how much you restrict calories. This, along with loss of walking, is in my opinion the hardest on the boys. Existing treatments cause a huge change in their appearance which is yet another thing that is completely out of their control. The swelling of the face which is called 'the moon face'; decreased bone density; problems controlling emotions – it's much harder for the boys to control their temper; trouble sleeping; and spots. These sides effects when read about can seem like very small issues, but for a current drug to give such harsh side effects for such a small benefit personally I think this makes them harder to deal with.

9a. If there are advantages of Vamorolone 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? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Vamorolone 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**	My son was on vamorolone for nearly six years. He was 11 when we had to stop using vamorolone and up until that time my son was doing amazingly. The weight gain was controllable if managed and monitored. My son started vamorolone in 2017 and by 2020 his weight had increased – but because it had been such a small gradual increase over the three years it had crept up bit-by-bit and we and his doctors only noticed at this point that it was hindering my son somewhat, so as a family we to make changes in diet like thins instead of bread, sweeteners instead of sugar and within 4-6 months had dropped the weight by around 15kg. My son at this point was doing fantastically for his age. Doctors and medical teams would comment regularly over how great he was doing for an 11-year-old. My son would only use his chair for long distances. He could still independently walk around school; around our home; from the school car park to his school; from our house down two steps to the drive to access the car. My son could walk around our home, dress himself, get a drink and a snack. He could take himself to the toilet without having to ask; he could get himself on and off the toilet but now has to have an adult dress him, shower him, help him on and off the toilet and get anything he needs. He could go take himself to his room, go for small walks and get in the garden. It's extremely hard to try and say which advantage I consider to be the most important as every last advantage was so important to us and mostly so important to my son but if I had to try my hardest to pick one it would be his loss of independence and ability to walk as this caused the biggest impact on him and the whole family and has by far been the most heart breaking for him.

	We had to come off vamorolone as we were offered a chance at another trial. This was one the hardest decisions we had to make but we decided to try and within three months of us changing to the standard NHS steroid my son could no longer walk, no longer do anything independently, suffered massive weight gain and more. This shows us what advantages vamorolone was giving to my son and it was heart breaking that we had to choose between the steroid that was working so well to a standard one that stripped my son of any independence within weeks.
10. If there are disadvantages of Vamorolone over current treatments on the NHS please describe these. For example, are there any risks with Vamorolone? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Not that I am aware of or have come across with our own personal experience
11. Are there any groups of patients who might benefit more from Vamorolone or any who may benefit less? If so, please describe them and explain why 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	
12. What influences patient and caregiver preferences when considering different treatments for DMD?	From a caregiver point of view, I would travel the world to access a treatment that could help my son. There would be nothing I would not do. The safety aspect is extremely important to me as a mum; a treatment that could prolong life most importantly and something that could keep as much muscle function for as long as possible because this is the best thing for the boys and to keep them as independent as possible for as long as possible. I asked my son this question as I think his view is most important. He said there is nothing he would not try, or no distance that would put him off having a treatment

	but the thing that was most important to him was keeping him walking. Since coming off vamorolone this is no longer an option. He said the second thing was the less side effects the better. He said the way some medicines make you look is not nice. He said since coming of vamorolone he feels he looks so completely different and that makes him sad.
13. What are patients views on vamorolone potentially having reduced efficacy compared to other treatments in terms of muscle function outcomes but potentially an improved safety profile (for example reduced stunted growth and behavioural issues)**?**	I am not aware of any evidence that vamorolone is less effective than existing steroids and am concerned that this question might be misleading.
12. Are there any potential equality issues that should be taken into account when considering Duchenne muscular dystrophy and Vamorolone? Please explain if you think any groups of people with this condition are particularly disadvantage 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 More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Not that I am aware of or have come across with our own experience.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- My son's diagnosis of Duchenne muscular dystrophy completely upturned our family life; DMD is a devasting condition for those who live with it and their careers and loved ones.
- There is a huge lack of treatment options for Duchenne muscular dystrophy; this leaves families feeling helpless, angry and scared about the future.
- My sons experience of vamorolone has been hugely positive and the impact of coming off it in order to participate in a clinical trial has been incredibly difficult to witness; our personal experience is that vamorolone was a more effective treatment than corticosteroids and that it did not come with acute side-effects that have great distress to my son and our family.
- The impact of the side effects of corticosteroids cannot be overstated; when you read about them, they may seem like very small issues, but for a child or young man they are devastating and have the potential to disrupt all areas of an individual and a family's life.
- Duchenne families are faced with impossible decisions, with no right answer and a great amount of distress crated by the prospect of getting it wrong; having the option to choose a treatment with limited side-effects and better quality of life would be game changing for many families.

Thank you for your time.

NICE National Institute for Health and Care Excellence

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Vamorolone [ID4024]: For treating inflammation associated with Duchenne muscular dystrophy

A Single Technology Appraisal

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Author Contributions:

Alex Allen	Critical appraisal of the company's clinical effectiveness evidence and drafted sections of the report
Madhusubramanian Muthukumar	Critical appraisal of the company's economic evidence and analysis, conducted additional economic analyses, and drafted sections of the report
Brian O'Toole	Project manager. Critical appraisal of the company's economic evidence and analysis, and drafted sections of the report.
Alan Lovell	Project manager. Critical appraisal of the company's literature search strategies and editorial input.
Imelda Hughes	Expert clinical advice to the EAG about DMD and its treatment

Author Contributions:	
Anirban Majumdar	Expert clinical advice to the EAG about DMD and its treatment
Caroline Farmer	Critical appraisal of the company's clinical effectiveness evidence and editorial input.
Edward C. F. Wilson	Project director. Conducted additional economic analyses and drafted sections of the report

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Abbreviations

Acronym	Definition
6MWT	Six-minute walk test
ACE	Angiotensin-converting enzyme
AE	Adverse effect
AESI	Adverse event of special interest
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BOI	Burden of illness
CEA	Cost effectiveness analysis
CEM	Coarsened exact matching
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for AEs
DMD	Duchenne muscular dystrophy
DNHS	Duchenne Natural History Study
EAG	External Assessment Group
EEACT	Economic Evaluation alongside Clinical Trials
EMA	European Medicines Agency
FDA	Food and Drug Administration
FVC	Forced Vital Capacity (expressed as % of predicted)
GC	Glucocorticoid
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTMF	Hand-to-mouth function
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IxRS	Interactive voice/web Response System

Acronym	Definition
KM	Kaplan Meier
LSM	Least squares mean
LYG	Life years gained
MAR	Missing at random
MCID	Minimal clinically important different
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intention to treat
MMRM	Mixed model repeated measures
MNAR	Missing not at random
NA	Not applicable
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NH	Natural history
NHB	Net Health Benefit
NHM	Natural history model
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NSAA	North Star Ambulatory Assessment
NSUK	North Star UK
OWSA	One-way sensitivity analyses
PARS	Psychosocial Adjustment and Role Skills
PAS	Patient access scheme
PD	Pharmacodynamic
PICO	Population Intervention Comparator Outcome
PIP	Paediatric investigational plan
PK	Pharmacokinetic
PODCI	Paediatric Outcomes Data Collection Instrument
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	Quality assessment

Acronym	Definition
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse effect
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SoC	Standard of care
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAE	Treatment-emergent adverse events
TSQM	Treatment Satisfaction Questionnaire
TTCLIMB	Time to climb four stairs
TTRW	Time to run or walk 10 metres
TTSTAND	Time to stand from supine
UK	United Kingdom

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External 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.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3 to 1.6.

Broadly speaking, the key clinical issues related to the company's conclusion that vamorolone is equally effective as prednisone (SoC) and a lack of evidence linked to the sequencing of glucocorticoid treatments. In terms of cost effectiveness issues, the EAG noted that there was uncertainty surrounding: the company's approach to modelling standard of care (SoC); the estimation of the proportion of patients remaining on treatment over time; and the long-term impact of vamorolone on outcomes, particularly growth. The EAG also questioned the appropriateness of the stopping rule for vamorolone. Finally, the company's base case included a number of non-reference case items when estimating health state costs.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
#1	The EAG disagreed with the company's conclusion that vamorolone was equally effective as existing treatments	3.2.3.1, 3.5, 4.2.6
#2	Children on DMD may change steroid treatment due to efficacy and adverse effects, but treatment sequencing has not been included in the economic model	2.4, 3.2.2.2, 3.2.3.2, 3.5

ID	Summary of issues	Report sections
#3	The use of a blended comparator created uncertainty in cost effectiveness estimates	4.2.4, 6.2.2, 6.3
#4	There was inconsistency in efficacy assumptions between vamorolone and SoC following dose reduction	4.2.6, 6.3
#5	There was uncertainty about long-term discontinuation rates for vamorolone	3.2.2.2, 3.2.3, 4.2.6, **Error! Reference source not found.**, 6.3
#6	There was uncertainty over long-term stunted growth and behavioural outcomes following vamorolone	3.2.3, 4.2.6, 6.2.6, 6.3
#7	The company used a 1.7x QALY severity multiplier in the model, while the EAG believed that a 1.2x multiplier was more appropriate	4.2.6, 6.2.7, 6.3, 7
#8	The company included a large number of out-of-scope / non-reference case costs in its base case analysis for health state costs	4.2.8, 6.2.9, 6.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
The use of a blended comparator and the definition of SoC (85:15 pred:def) not applied consistently	Company assumed a blended comparison for SoC which consisted of 85% receiving prednisone and 15% receiving deflazacort. However, it has not been consistently applied across drug costs and adverse events in the model.	The EAG preferred to compare vamorolone to each individual treatment in a fully incremental analysis.	1.2, 1.5, 4.2.4, 6.2.2, 6.3
Limited short-term trial data on vamorolone discontinuation	The company's base case accounted for vamorolone discontinuation based on VISION-DMD short-term (<1 year) trial data, which is subject to high uncertainty in the long term.	The EAG assumed that the proportion of patients discontinuing vamorolone would be the same as CINRG data for deflazacort in the long term	1.2, 1.5, 4.2.6, 6.2.4, 6.3
Parametric extrapolation of proportion of patients	In the company's base case analysis, the proportion of patients on vamorolone and SoC were estimated by fitting independent Log-	EAG's preferred assumption implemented Generalised gamma parametric modelling to the proportion of patients discontinuing treatments.	1.2, 1.5, 4.2.6, **Error! Reference source not found.**, 6.3

	Company's preferred assumption	EAG preferred assumption	Report Sections
discontinuing vamorolone	logistic curves to each treatment arm.		
Down-titrated dose efficacy	In the company's base case, reduced transition probabilities were applied to people receiving SoC who had a dose reduction, whilst no reduction in effectiveness was applied to down-titrated vamorolone.	EAG's preferred assumption was to apply reduced effectiveness to reduced doses for both SoC and vamorolone. Modelling limitations meant the EAG eliminated the reduced effectiveness in SoC rather than applying the reduction to vamorolone.	1.2, 1.5, 4.2.6, 6.3
The proportion of vamorolone patients experiencing adverse events	The company assumed that the proportion of patients on vamorolone with stunted growth was 0% (based on 24-week data from VISION DMD).	Due to the lack of robust long-term clinical data, the EAG preferred to assume that a small proportion of patients on vamorolone (10% for All AESI and 5% for moderate/severe AESI) will experience stunted growth and 5% will experience behavioural issues as moderate/severe AESI.	1.2, 1.5, 4.2.6, **Error! Reference source not found.**, 6.3
Cost items	The company included non-medical and indirect costs in base case, and included of growth hormone costs	The EAG's preferred approach was the inclusion of only NHS+PSS costs, as per NICE reference case, and the exclusion of growth hormone costs on the basis of clinical opinion.	
QALY multiplier	1.7x was applied in the company's modelled base case	The EAG preferred to apply 1.2x in the EAG base case	1.2, 1.5, 4.2.6, 6.2.13, 6.3, 7

Abbreviations: AESI, Adverse event of special interest; CINRG, Cooperative International Neuromuscular Research Group; EAG, External Assessment Group; NHM, natural history model; QALY, quality-adjusted life year; SoC, standard of care

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:

- Reducing the number of adverse/acute events compared to SoC, thereby improving HRQoL and lengthening time on treatment.

Overall, the technology is modelled to affect costs by:

- Adding acquisition costs of vamorolone to the treatment pathway
- Offsetting downstream costs by reducing the number of adverse effects and their treatment costs (such as the use of growth hormone for stunted growth or the need for spinal surgery following vertebral fracture)

The modelling assumptions that have the greatest effect on the ICER are:

- Fully incremental comparison of vamorolone with prednisone and deflazacort (rather than a blended comparison)
- The rate of discontinuation of treatment for people using vamorolone and its parametric extrapolation in the long term
- The application of a symmetric effect of reduced dosing
- The rate of stunted growth and behavioural issues related moderate/severe AESI events with vamorolone in the long term

1.3. The decision problem: summary of the EAG's key issues

The EAG noted that a number of scoped outcomes for this appraisal were not captured in the evidence base for vamorolone. While the EAG considered that the absence of some of these outcomes led to uncertainty in the clinical effectiveness of vamorolone, clinical experts to the EAG advised that the outcomes available would be sufficient to determine whether vamorolone was effective and safe in the short term. The EAG therefore did not identify any key issues regarding the decision problem for this appraisal.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the clinical effectiveness and safety evidence presented in the CS and identified the following key issues for consideration by the committee.

Key Issue 1: The EAG disagreed with the company's conclusion that vamorolone was equally effective as existing treatments

Report sections	**3.2.3.1, 3.5, 4.2.6**
Description of issue and why the EAG has	In Section B.3.3.2 of the CS, the company suggested that vamorolone 6.0 mg/kg/day showed comparable efficacy to prednisone 0.75 mg/kg/day in

Report sections	3.2.3.1, 3.5, 4.2.6
identified it as important	VISION-DMD. The company used this conclusion to drive assumptions in its economic model. The EAG did not agree with this interpretation of the VISION-DMD data. Prednisone 0.75 mg/kg/day offered a benefit over vamorolone 6.0 mg/kg/day at 24 weeks for several clinical outcomes related to muscle function. These differences were interpreted by the EAG as being clinically meaningful to people with DMD. Therefore, the EAG considered that prednisone 0.75 mg/kg/day was consistently more effective than vamorolone 6.0 mg/kg/day for the efficacy outcomes reported, and an assumption of comparable efficacy was inappropriate.
What alternative approach has the EAG suggested?	The EAG considered that vamorolone may still be a valued treatment option for people with DMD, despite the potential risk that it may have poorer clinical outcomes related to muscle function. This was based on the understanding that vamorolone offers an alternative safety profile, that may be preferred for some people with DMD. Within the context of this appraisal, this key issue has more significant implications for the company's model, which did not capture the difference in clinical efficacy between vamorolone and SoC. The EAG was unable to address this during its appraisal.
What is the expected effect on the cost-effectiveness estimates?	If the company's model was amended to incorporate a clinical advantage for SoC, this would reduce the QALY gain for vamorolone and would be expected to substantially increase the ICER
What additional evidence or analyses might help to resolve this key issue?	Further comparative evidence between vamorolone and SoC, particularly at longer follow-up and including outcomes that assess the implications of any difference in clinical efficacy between arms, would provide clarity on any difference in treatment efficacy between arms. The EAG was aware that the company had conducted an indirect treatment comparison between VISION-DMD and another trial that evaluated SoC options, though only reported safety outcomes. If the company were able to provide a comparison of clinical outcomes from this analysis, that may provide further data beyond the 24-week comparison available in VISION-DMD. With regards to the economic model, the company could address this by utilising transition probabilities for vamorolone linked to the efficacy in the VISION-DMD trials rather than using those developed from the natural history model (NHM) dataset. The company noted in Section B.3.3.2 of the CS that this was not feasible due to the short follow-up of 24 weeks. However, the company could investigate approaches to extrapolation that were more suitable than using the NHM transition probabilities or alternatively applying the efficacy difference between vamorolone and prednisone in the VISION-DMD to the transition probabilities in the NHM.

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; CS, company submission, EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; MCID, minimal clinically important difference; NHM, natural history model; QALY, quality-adjusted life year; SoC, standard of care; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine.

Key Issue 2: Children on DMD may change steroid treatment due to efficacy and adverse effects, but treatment sequencing has not been included in the economic model

Report sections	**2.4, 3.2.2.2, 3.2.3.2, 3.5**
Description of issue and why the EAG has identified it as important	The decision of whether to use prednisone/prednisolone or deflazacort as the initial therapy for DMD is largely based on parent preferences related to the expected efficacy and side effects for each treatment (and the broader health and wellbeing of the person with DMD). Typically, prednisone/prednisolone is associated with weight gain, increased appetite, and behavioural problems, while deflazacort is thought to lead to eye cataracts, a higher risk of stunted growth and extremely delayed puberty. Based on the CS, the EAG considered that vamorolone may be less effective than SoC but may have an improved safety profile for some adverse events. The EAG considered it plausible that vamorolone would be received at varying lines of treatment, depending on parent preferences. However, trial evidence for vamorolone is based on a treatment-naïve population and the EAG was unable to determine whether the effect of vamorolone would vary according to its positioning. In addition, the economic model was not structured to allow people to have a sequence of glucocorticoid treatments for DMD.
What alternative approach has the EAG suggested?	The EAG was unable to address this issue, given the VISION-DMD trial design and the structure of the company's economic model.
What is the expected effect on the cost-effectiveness estimates?	Given the lack of available evidence for varying treatment effects according to treatment line and the format of the company's model, the EAG was unable to speculate on the potential impact of this key issue on cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Within the timeframe of this appraisal, the EAG was unable to identify data points for clinical outcomes following treatment switching between prednisone and vamorolone in VISION-DMD, as these were not presented in the CS (aside from in charts). If the company was able to provide data for these outcomes, the EAG may be able to appraise their comparability with treatment outcomes in the first line population. However, the EAG was aware that these data would still be a partial and limited evaluation of this issue. Input from clinical experts as to whether treatment outcomes with SoC vary according to treatment line may be able to provide clarity on this issue. It would not be feasible to evaluate the impact of treatment sequences on cost effectiveness outcomes without structural changes to the company's economic model.

Abbreviations: EAG, External Assessment Group; DMD, Duchenne muscular dystrophy; SoC, standard of care.

1.5. The cost effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the cost-effectiveness and wider economic evidence presented in the CS and identified the following key issues for consideration by the committee.

Key Issue 3: The use of a blended comparator created uncertainty in cost effectiveness estimates

Report sections	4.2.4, 6.2.2, 6.3
Description of issue and why the EAG has identified it as important	In the company's base case analysis, the primary comparator was SoC, which was assumed to be a mixture of prednisone and deflazacort. For the estimation of drug costs, the split was assumed to be 85% for prednisone and 15% for deflazacort. However, this split was not used consistently for the estimation of adverse/acute events, vertebral fractures, and spinal surgeries. As such, there was dissonance between the company's modelling of comparator treatment costs and their approach to modelling impact of adverse/acute events, vertebral fractures, and spinal surgeries. Clinical expert opinion to the EAG also noted that prednisone and deflazacort have distinct safety profiles, suggesting that it may be more appropriate to capture the adverse event impact of each treatment separately in the model, where possible. Therefore, the EAG did not consider that the company's approach to modelling the comparators in a blended way was appropriate, as it ignored the differences between prednisone and deflazacort in terms of their efficacy and safety profiles, adds uncertainty to the results and potentially biases the analysis in favour of vamorolone.
What alternative approach has the EAG suggested?	Where possible within the current model framework, the EAG compared vamorolone to each corticosteroid separately. This allowed for a relatively clear distinction of safety profile between SoC treatments and reduced the associated uncertainty as part as was feasible. This was considered as part of the EAG preferred base case. Clinical expert opinion to the EAG was that, in clinical practice in the NHS, there was an approximately 50/50 split in the use of prednisone and deflazacort. The EAG therefore conducted a scenario analysis using a blended comparator treatment split of 50% prednisone and 50% deflazacort, though, overall, retained its preference for separate comparators.
What is the expected effect on the cost-effectiveness estimates?	A tangible increase in the ICER was observed, mainly owing to the differences in safety between prednisone and deflazacort. This was seen despite similar drug acquisition costs and clinical efficacy assumptions between the SoC treatments.
What additional evidence or analyses might help to resolve this key issue?	Providing an individual comparison of vamorolone versus prednisone and deflazacort using respective clinical efficacy and adverse event data would help to resolve the uncertainty further.

Abbreviations: EAG, External Assessment Group; GC, glucocorticoid; ICER, Incremental cost-effectiveness ratio; SoC, standard of care.

Key Issue 4: There was inconsistency in efficacy assumptions between vamorolone and SoC following dose reduction

Report sections	4.2.6, 6.3
Description of issue and why the EAG has	The company's base case applied proportionally reduced transition probabilities for SoC patients who were on treatment following a dose reduction but did not apply this to vamorolone patients who similarly down-

Report sections	**4.2.6, 6.3**
identified it as important	titrated. The EAG considered this asymmetry to be inappropriate and to overestimate the QALY gain from vamorolone whilst reducing its cost.
What alternative approach has the EAG suggested?	The EAG applied SoC efficacy and transition probabilities for patients who down-titrated on SoC in line with the assumption for vamorolone (i.e., no impact on efficacy from down-titration). The EAG acknowledged that, in reality, there would likely be a reduction in efficacy following down titration with SoC and vamorolone, but due to the structure of the model there was no robust way of implementing this. This was implemented in the model by setting the proportion on treatment receiving full efficacy to the same as the proportion on treatment for the SoC arm (in a similar way to how it was implemented for vamorolone in the company's modelled base case).
What is the expected effect on the cost-effectiveness estimates?	This change resulted in an increase of health state related QALY gain for the SoC arm, thereby causing a reduction in incremental QALYs and a tangible upward impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Availability of long-term studies on efficacy of reduced dosing of SoC could help to reduce this uncertainty further.

Abbreviations: EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Key Issue 5: There was uncertainty about long-term discontinuation rates for vamorolone

Report sections	**3.2.2.2, 3.2.3, 4.2.6,** Error! Reference source not found.**, 6.3**
Description of issue and why the EAG has identified it as important	The EAG noted that data for the number of people who discontinue vamorolone were only available for a short duration (<1 year), based on the VISION-DMD trial data. There was therefore some uncertainty in the likely discontinuation rate beyond this time. The company's method for extrapolating these short-term data provided some advantage for vamorolone in the model, which the EAG did not consider was justified on the basis of the evidence available. This uncertainly was especially acute given that the comparator arm (SoC) had discontinuation data available for ~14 years, derived from CINRG. Also, in the company's modelled base case analysis, the proportion of patients on vamorolone and SoC were estimated by fitting independent Log-logistic curves to each treatment arm. However, the EAG considered generalised gamma to be best fitting curve for SoC, given it aligned more closely with prednisone and deflazacort KM data. This was implemented as part of the EAG preferred base case as this was linked to the treatment discontinuation data used for the modelled EAG base case.
What alternative approach has the EAG suggested?	The EAG assumed that the proportion of patients discontinuing vamorolone would be the same as CINRG data for deflazacort in the long term. Deflazacort arm data was chosen as its KM curve closely resembled that of vamorolone (based on EAP data presented in the clarification response) and improved adherence might be expected given the claim of better side effect profile for vamorolone.

Report sections	**3.2.2.2, 3.2.3, 4.2.6,** Error! Reference source not found.**, 6.3**
	In terms of the parametric fit, the EAG implemented generalised gamma modelling of the proportion of patients discontinuing treatments and applied deflazacort discontinuation data based on CINRG for vamorolone.
What is the expected effect on the cost-effectiveness estimates?	This change substantially increased the ICER due to the higher proportion of patients remaining on vamorolone in the long term. This was despite the generalised gamma curve predicting a slightly lower proportion of patients discontinuing with time across treatment arms, resulting in increased treatment costs for vamorolone as well as the health state related QALY gain. However, the net effect was increased incremental costs, which could not be offset by the corresponding increase in the incremental QALYs, thereby resulting in an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	Long-term treatment discontinuation data for vamorolone would help address this uncertainty.

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Key Issue 6: There was uncertainty over long-term stunted growth and behavioural outcomes following vamorolone

Report sections	**3.2.3, 4.2.6,** Error! Reference source not found.**, 6.3**
Description of issue and why the EAG has identified it as important	Stunted growth and behavioural issues are known side effects of existing SoC for DMD. In the company's base case, 72% of patients in the SoC arm were modelled to experience stunted growth, as opposed to 0% of patients in the vamorolone arm. This was based on 24-week data reported in VISION-DMD. Additionally, 0% of patients on vamorolone were modelled by the company to have behavioural issues as moderate/severe adverse events (also based on 24-week data from VISION-DMD). The EAG considered there to be some uncertainty surrounding these assumptions, given that they were based on short-term follow-up. Clinical advice to the EAG also noted that stunted growth could manifest in later years of life.
What alternative approach has the EAG suggested?	In the absence of robust long-term data, the EAG opted to assume that a small proportion of patients on vamorolone (10% for All AESI and 5% for moderate/severe AESI) will experience stunted growth and 5% will experience behavioural issues as moderate/severe AESI. These assumptions were included as part of the EAG's preferred base case. The EAG also conducted a scenario analysis with the vamorolone arm having the same proportion of stunted growth and behavioural issues as with SoC. This was considered to be a worst-case scenario, compared to the company's modelled base case, which presented the best-case scenario (that of a proportion of 0%). These two scenarios therefore provided an upper and lower bound, with the most plausible values lying in-between.
What is the expected effect on the cost-	The EAG observed that this change increased the ICER moderately, due to the modelled cost and disutility associated with stunted growth and behavioural issues.

Report sections	**3.2.3, 4.2.6,** Error! Reference source not found.**, 6.3**
effectiveness estimates?	
What additional evidence or analyses might help to resolve this key issue?	Longer term clinical data reporting the impact of vamorolone on patient growth and behaviour, or other impactful AEs, would help to resolve this uncertainty.

Abbreviations: AESI, Adverse event of special interest; DMD, Duchenne muscular dystrophy; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; SoC, standard of care

Key Issue 7: The company used a 1.7x QALY severity multiplier in the model, while the EAG believed that a 1.2x multiplier was more appropriate

Report sections	**4.2.6, 6.2.13, 6.3, 7**
Description of issue and why the EAG has identified it as important	The company's base case used a 1.7x QALY multiplier, based on an absolute QALY shortfall of 18.02 years. The EAG believed that this was subject to high uncertainty and noted that it had a substantial impact on the cost-effectiveness results. Also, the expected total QALYs for the general population were derived using EQ-5D-3L while the total QALYs for people living with the condition receiving SoC were derived using DMD-QoL. Given the different QoL instruments used, one being generic and the other being disease specific, this further increased the uncertainty in the QALY shortfall estimate.
What alternative approach has the EAG suggested?	Given the high uncertainty around the modifier and the likelihood of QALY shortfall falling between 12-18 years in the EAG base case, a QALY multiplier of 1.2x was considered. The EAG also conducted a scenario analysis with 1x QALY multiplier, as there was a chance that the absolute QALY shortfall would fall below 12 years, given the associated uncertainties.
What is the expected effect on the cost-effectiveness estimates?	Reducing the QALY multiplier from 1.7 to 1.2 substantially increased the ICER due to reduction in the incremental QALY gain.
What additional evidence or analyses might help to resolve this key issue?	Availability of mapping between DMD-QoL and EQ-5D-3L, might help to resolve this uncertainty further.

Abbreviations: EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Key Issue 8: The company included a large number of out-of-scope / non-reference case costs in its base case analysis for health state costs

Report sections	**4.2.8, 6.2.11, 6.3**
Description of issue and why the EAG has identified it as important	The NICE reference case specifies that cost perspective should be that of the NHS and personal social services (PSS) only. The company's costings for its reference case, however, included additional costs such as patient out of pocket costs (OTC medications, transport and alternative and complementary

Report sections	4.2.8, 6.2.11, 6.3
	therapies) and transfer payments (described as direct non-medical costs, Section B3.5.2, CS).
What alternative approach has the EAG suggested?	The EAG approach excluded out-of-scope costs, to limit the perspective to the NICE reference case.
What is the expected effect on the cost-effectiveness estimates?	The approach could bias the ICER either upwards or downwards, depending on the relative time spent in different health states in each arm.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence was required. The EAG modified the costs in its base case, limiting them to NHS and PSS costs only.

Abbreviations: CS, company submission; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

1.6. Other key issues: summary of the EAG's views

No other key issues were identified.

1.7. Summary of EAG's preferred assumptions and resulting ICER

Table 3 summarises the corrections (mainly to the severity modified QALYs and other corrections as mentioned in Section 6.1) and EAG-preferred changes to the company base case analysis, and their isolated and collective implications for cost-effectiveness results. The EAG's adjustments collectively reduced the expected incremental QALY gain associated with vamorolone while increasing its expected incremental cost, leading to EAG-preferred ICERs that were far in excess of the relevant NICE decision-making threshold range.

Table 3: Summary of EAG's preferred assumptions and ICER

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)
EAG corrected company base case					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symmetric impact of down-titration of treatment dose					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% stunted growth and behavioural issues with vamorolone in long-term					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation extrapolated using gen-gamma with vamorolone discontinuation assumed same as deflazacort CINRG data					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude out-of-scope costs					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude growth hormone costs					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.2x QALY multiplier applied					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (deterministic)					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (probabilistic)					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

This report contains the EAG's assessment of the company submission (CS) submitted for the Single Technology Appraisal (STA) of vamorolone (Agamree®, Santhera) for treating Duchenne muscular dystrophy in people aged four years and older.

2.2. Critique of the company's description of the underlying health problem

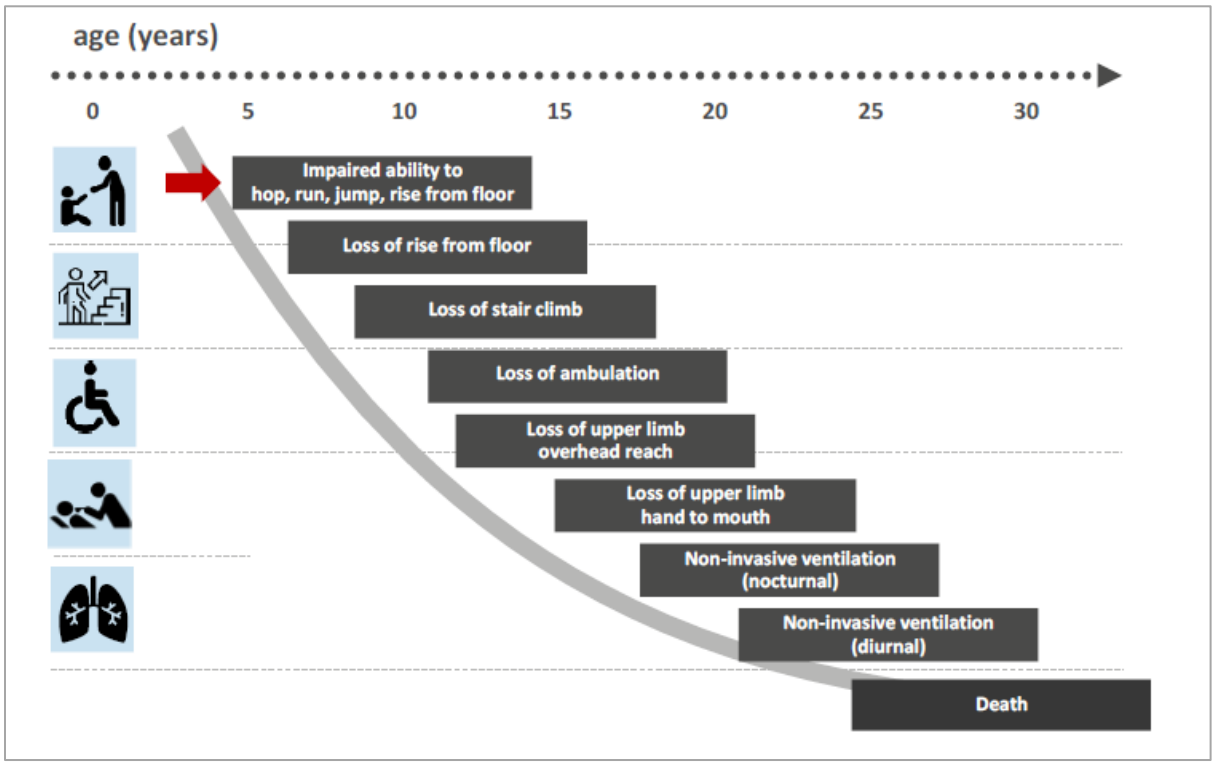
The EAG agreed with the company's description of Duchenne muscular dystrophy (DMD). In brief, DMD is a genetic disorder characterised by progressive muscle degeneration and weakness due to the alterations of a protein called dystrophin that helps keep muscle cells intact. This faulty gene can itself be caused by a range of genetic causes, such as deletions or duplications, point mutations, and nonsense mutations. The EAG's clinical experts advised that it is important to know exactly where the mutation is and what type of mutation it is to guide treatment. For example, people with DMD caused by the nonsense mutations are eligible for ataluren, in addition to standard of care.[1] Because the dystrophin gene is found on the X-chromosome, it primarily affects males, while females are typically carriers. However, some females can manifest varying ranges of physical symptoms of Duchenne and are therefore called "manifesting carriers".

DMD symptom onset is in early childhood, usually between ages 2 and 3. People with DMD begin to experience a decline in muscle strength in their hips and legs, leading to a loss of abilities such as running, climbing stairs, getting up from a lying position, and eventually, walking or bearing weight. As muscle strength decreases, weakness will spread to the arms and neck and over time, paralysis will set in, with the loss of arm and hand-function. Young adults can develop dysphagia, resulting in difficulty chewing and swallowing food and requiring a feeding tube. They will need help with all self-care activities, including eating, drinking, toileting, dressing, washing, being moved into bed, and being turned in bed. Respiratory function will also weaken as DMD progresses, leading to assisted ventilation, and the heart muscle will be affected, leading to cardiac failure. In Section B.1.3, the company highlighted the significant disease-related burden for patients, families and caregivers in terms of physical, health demands, logistical, emotional, psychological, and financial burden. Given that symptoms can

start presenting in children as young as two years old, people with DMD live their whole life with gradually increasing physical impairment and dependency on other people.

The company detailed the natural history of a person diagnosed with DMD who is treated with glucocorticoids in Figure 1 below. The aim of glucocorticoid treatment is to slow the progression of disease, and delay a person's loss of ambulation, ability to self-feed, and need for assisted ventilation.

Figure 1: Typical muscle degeneration seen in patients with DMD



Source: CS, Figure 2, Document B

2.3. Critique of the company's overview of current service provision

The company detailed the clinical pathway of care in Section B.1.3 of the CS. The EAG's clinical experts agreed with the company that DMD is a progressive disease and treatment goals are aimed at delaying disease progression for as long as possible, and to anticipate and manage the associated complications, such as joint contractures, scoliosis, bone fractures, cardiomyopathy, respiratory insufficiency and treatment-related adverse events (AEs).

The EAG agreed with the company that the current standard of care for DMD is glucocorticoids, specifically prednisone/prednisolone or deflazacort. Glucocorticoids have demonstrated significant benefits in minimising the progressive loss of muscular strength and consequently extending ambulatory function, avoiding scoliosis surgery, preserving upper limb function and delaying the start of cardiac and respiratory function decline. However, they are associated with severe side effects, which include osteoporosis, reduced bone strength and increased risk of vertebral fractures, resulting from the potent osteotoxicity of glucocorticoid therapy combined with progressive myopathy. The EAG's clinical experts advised that treatment with glucocorticoids currently starts in children at a point after they have turned four years old. The decision of whether to use prednisone/prednisolone or deflazacort is taken by the child's parents and is largely based on preferences related to the balance between the expected efficacy and side effects for each treatment. Typically, prednisone/prednisolone is associated with weight gain, increased appetite, and behavioural problems, while deflazacort is thought to lead to a longer period of ambulation, but with the risk of stunted growth and extremely delayed puberty. The EAG's clinical experts noted that people with DMD often have learning difficulties and autism spectrum disorders, and behavioural problems caused by prednisone may be exacerbated by the underlying disorders. In that case parents may choose to initially choose deflazacort treatment rather than prednisolone. However, parents can change the glucocorticoid and dose of glucocorticoid in response to adverse events. Notably for this appraisal, the EAG's clinical experts estimated that 50% of new prescriptions of glucocorticoids in the DMD population in the UK are for prednisolone and 50% are for deflazacort. The EAG's clinical experts advised that a very small proportion of parents of people with DMD may decline glucocorticoid treatment at the outset.

Aside from glucocorticoids, children may also receive vitamin D and gastroprotectives, such as ranitidine or omeprazole. There are other treatments, such as antisense oligonucleotides (ASOs) or monoclonal antibody therapy. These treatments are not suitable for all with DMD as they are exon skipping specific and their efficacy is currently unclear in the DMD population.

Glucocorticoid treatment has been shown to be effective at delaying the loss of ambulation in people with DMD: this can occur at around 10 years old in untreated children but it can occur more than two years later in those on glucocorticoid treatment.[2] The EAG's clinical experts noted that the primary reason for offering glucocorticoids to people with DMD is to prolong ambulation, and after loss of ambulation treatment can be reduced or withdrawn. In the CS, the company stated that glucocorticoid treatment can continue after loss of ambulation. The EAG

understood that in some occasions, treatment with glucocorticoids may be reduced rather than withdrawn because it may protect them from scoliosis and slow down both cardiomyopathy and decline in respiratory function.

The EAG's clinical experts advised that once children lose ambulation, care is taken to closely monitor their spines, sleep-disordered breathing and heart. The spine develops scoliosis, which needs its own management and may require scoliosis surgery. The heart develops cardiomyopathy, which may need treatment with ACE inhibitors and beta blockers. Sleep studies can be used to assess the development of respiratory failure. People will then require overnight non-invasive ventilation and cough assist to help clear their airways.

2.4. Critique of company's definition of decision problem

A summary of the decision problem for this appraisal, and the EAG's appraisal of how the CS addresses it, is shown in Table 4. The company positioned vamorolone as an alternative to glucocorticoids (prednisone/prednisolone or deflazacort) offered to people with DMD. As noted in Section 2.3, prednisone/prednisolone and deflazacort can offer significant benefits in slowing the progression of DMD but are also associated with severe adverse effects. The EAG's clinical experts stated that a drug that offered a similar benefit to prednisone/prednisolone or deflazacort in delaying loss of ambulation while having fewer significant adverse effects would be a valuable addition to the DMD treatment pathway.

The population for this appraisal began as people with DMD who are aged two years and older. However, after the company submission but prior to the clarification stage, marketing authorisation was granted by the European Medicines Agency (EMA) for vamorolone in people with DMD who are four years and older.[3] The MHRA is expected to grant marketing authorisation in line with the EMA decision, and the company updated the population for this appraisal. The EAG noted that the vamorolone trials used for this appraisal recruited children four years and older, and as such, provided evidence appropriate to the updated population in the appraisal.

The EAG noted that the children who were recruited to VISION-DMD were naïve to glucocorticoid treatment, while treatment line is not specified in the NICE scope for this appraisal or in the EMA marketing authorisation. The EAG's clinical experts were aware that people may receive vamorolone after previously receiving treatment with a different glucocorticoid, or alternatively might receive treatment with a different glucocorticoid after

previous treatment with vamorolone. The cost-effectiveness of treatment sequencing was not assessed in this appraisal or adequately explored in the pivotal trial (VISION-DMD). This issue is discussed further in Key Issue 2.

The company also stated that the population aged over 7 years of age is supported by an ongoing Phase II open-label, multiple dose trial (VBP15-006) to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with DMD. The EAG noted that no results were presented for VBP15-006 in the CS.

The intervention for this appraisal was consistent with the decision problem. The doses tested in the VISION-DMD, were in-line with the dose permitted in the EMA marketing authorisation.

The comparator in the final scope issued by NICE was established clinical management without vamorolone. The company interpreted this as standard of care (SoC) with either prednisone or deflazacort. The pivotal trial, VISION-DMD, compared daily vamorolone to daily prednisone and data specific to deflazacort was taken from other trials such as FOR-DMD.[4] The EAG's clinical experts stated that 50% of new prescriptions of glucocorticoids for DMD are deflazacort in the UK. The EAG understood that there were differences in efficacy and safety between prednisone and deflazacort and the comparison of deflazacort to vamorolone had not been explored in an RCT. The EAG did not consider that data collected in the prednisone arm of VISION-DMD to be a fair representation of outcomes experienced by people receiving SoC in the NHS. Specifically, outcomes in the CS may overestimate weight gain and behaviour problems and underestimate outcomes linked to eye cataracts and stunted growth. The company provided AESI and acute event rates for deflazacort from the FOR-DMD trial[4] at the clarification stage (Question B8), utilised fracture data from the Perera et al. (2016)[5] and stunted growth from Wong et al (2016)[6] to fill holes in the evidence space.

The final scope issued by NICE described 16 outcomes to be considered in the appraisal. The company stated that 7 of the 16 outcomes were directly measured in VISION-DMD but noted that lung and cardiac function were consequences of muscle function and time to wheelchair could be assessed through walking ability. The EAG's clinical experts advised that the outcomes collected in VISION-DMD represented the standard clinical outcomes used on a day-to-day basis and were appropriate given the stage of DMD of the participants in VISION-DMD.

Outcomes detailed in the scope that were not measured in VISION-DMD included, cardiac function, lung function, time to wheelchair, and time to scoliosis. VISION-DMD recruited children four to seven years old, and no loss of ambulation was expected in children until 10 years of age. Therefore, participants in the trial would not be expected to move to use of a wheelchair over the treatment period. People with DMD develop scoliosis after loss of ambulatory capacity and onset of wheelchair dependence for mobility. In addition, children diagnosed with DMD have a baseline cardiac assessment for an early cardiomyopathy, but close monitoring of heart and lungs does not occur until children lose ambulation. The EAG understood that the controlled trial period of VISION-DMD was 24 weeks in people with early DMD, and as such, the trial was not long enough to offer a robust estimate of cardiac function, lung function, time to wheelchair, or time to scoliosis.

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[7] in the NICE reference case. The company did collect the Paediatric Outcomes Data Collection Instrument (PODCI) as a measure of quality of life in VISION-DMD. Outcomes collected in VISION-DMD are further discussed in Section 3.2.2.5.

The company's economic analysis was broadly in line with the NICE reference case. The EAG's major concerns are summarised in the key issues tables, but of note was the use of a blended comparator (prednisone and deflazacort), rather than comparing these are distinct treatment alternatives. This risks obscuring true differences in cost and effect between discrete treatment strategies, and thus could bias estimates of the ICER. The company also included a number of non-reference case costs (e.g., out of pocket costs, transport, and transfer payments) in its base case. The EAG therefore explored the impact of excluding these in the scenario analyses.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Vamorolone for treating Duchenne muscular dystrophy.	Treatment of DMD in patients aged 4 years and older.	The population aged 4 to 7 years of age is supported by VISION-DMD and VBP15-LTE studies presented in B.2.3. Summary of methodology of the relevant clinical effectiveness evidence. The population aged over 7 years of age is supported by an extrapolation report that includes Population Pharmacokinetics and Pharmacokinetics / Pharmacodynamics models as well as an ongoing Phase II Open-Label, Multiple Dose Study (VBP15-006) to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with DMD.	The population addressed in the CS was people with DMD aged 2 years and older. Marketing authorisation was granted for people with DMD aged 4 years and older and the company updated the submission at the clarification stage to reflect this. The children recruited to VISION-DMD were naive to glucocorticoid treatment and were aged 4 to 7 years old. Therefore, they represented the population of children having initial treatment for DMD but do not represent older children who may have had years of treatment with prednisone/prednisolone or deflazacort for DMD.
Intervention	Vamorolone.	Vamorolone.	Not applicable.	The two interventions used in the pivotal trial (VISION-DMD) were vamorolone at 2.0 mg/kg/day and vamorolone at 6.0 mg/kg/day. The EMA granted marketing authorisation for vamorolone up to 6.0 mg/kg/day for DMD.[3]
Comparator(s)	Established clinical management without vamorolone.	Established clinical management without vamorolone i.e., glucocorticoids, as per the clinical pathway of care	Not applicable.	The company interpreted SoC as management with glucocorticoids. Clinical expert advice to the EAG was that the glucocorticoids used for DMD in

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		presented in B.1.3. Health condition and position of the technology in the treatment pathway		the UK were approximately 50% prednisone/prednisolone and 50% deflazacort. The VISION-DMD trial used prednisone as the active comparator. The EAG understood that there were differences in the efficacy and safety profile of prednisone and deflazacort and the EAG was concerned that the pivotal trial did not include a deflazacort comparator arm.
Outcomes	• Walking ability (ambulation) • Muscle function • Muscle strength • Ability to undertake activities of daily living • Bone function • Cardiac function • Concordance and optimisation of treatment • Endocrine function • Lung function • Time to wheelchair • Number of falls • Time to scoliosis • Upper body function • Mortality • Adverse effects of treatment	• Walking ability (ambulation) • Muscle function • Muscle strength • Bone function • Concordance and optimisation of treatment • Adverse effects of treatment • Health-related quality of life (for patients and carers)	Some outcomes were not recorded in the key studies of vamorolone. Both lung function and cardiac function are consequences of muscle function and time to wheelchair can be assessed through walking ability; both are presented as part of the study outcomes. A conservative estimate of equal mortality to steroids has been assumed within the model.	The EAG's clinical experts advised that the function outcomes collected in VISION-DMD represented the standard clinical outcomes used on a day-to-day basis. Clinical expert advice to the EAG was that those outcomes not assessed in the clinical trial were relevant to DMD but would not be expected to occur in the age group and follow-up used in the company's trials. The company did not collect health-related quality of life data using EQ-5D, but did collect the Paediatric Outcomes Data Collection Instrument (PODCI) as a measure of quality of life.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Health-related quality of life (for patients and carers)			
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. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	A cost-utility analysis was conducted in Excel using the Project HERCULES model framework. QALYs were used to capture the health benefit of treatment and results were presented using the Incremental Cost Effectiveness Ratio (ICER), as appropriate. The time horizon used in the model was 50 years, which was considered long enough to capture the differences in costs and benefits between treatments. Costs were considered from an NHS and PSS perspective. Direct health effects for patients and caregivers were considered. Wider societal costs including productivity losses to the patient and unpaid carers were also considered.	Wider societal costs including productivity losses are important to capture as most DMD patients are cared for on a day-to-day, long-term basis by a combination of formal caregivers (paid), family members and informal caregivers (i.e., non- professional, unpaid). Because the loss of function increases as DMD progresses, the care of DMD patients also increases over time with 24/7 care once patients are on full-time ventilation.	Overall, the EAG considered the company's economic analysis was broadly aligned with the NICE scope. However, a number of out of scope cost items were included in the company's estimate of NHS+PSS costs. The cost associated with diagnostic testing was not included in the company's base case. The company also implemented a blended comparator (prednisone/deflazacort) which may obscure the true incremental cost-effectiveness of vamorolone.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups	Not specified in the scope	Not applicable.	Not applicable.	Not applicable.
Special considerations including issues related to equity or equality	Not specified in the scope	Not applicable.	Not applicable.	Not applicable.

Abbreviations: AESI, Adverse events of special interest; CS, company submission; DMD, Duchenne muscular dystrophy; EAG, External Assessment Group; EMA, European Medicines Agency; EQ-5D, European Quality of Life 5 Dimensions; HERCULES, Health Research Collaboration United in Leading Evidence Synthesis; ICER, Incremental cost-effectiveness ratio; kg, kilograms; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; mg, milligrams; PODCI, Paediatric Outcomes Data Collection Instrument; PSS, Personal Social Services; QALY, quality-adjusted life year; SoC, standard of care.

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify RCTs that have measured the efficacy and safety of treatments for people with Duchenne muscular dystrophy (DMD). A combined literature search strategy was used to identify clinical effectiveness evidence, adverse effects, cost effectiveness evaluations, HRQoL, and cost and resource use data.

The EAG noted some limitations to the searches undertaken for the SLR. The search strategies utilised thesaurus terms to describe interventions rather than free text terms – it is standard practice to use both subject headings combined with free text terms to conduct a comprehensive search. Without free text terms the search may have missed articles not yet indexed, or poorly indexed. The reporting of the searches was also unclear, with timepoints and numbers mismatched between the text and PRISMA diagram. There was also a lack of clarity in how the company searched for and selected studies used to inform parameters in the model (see section 4 for more details). The EAG was not aware of any efficacy studies that were missed in the search, but because of the limitations described, there was a chance that relevant studies were missed. This chance may be greater for studies included in the company's SLR that did not evaluate vamorolone, such as studies used to inform assumptions in the company's economic analysis.

In general, the EAG agreed with the company's principal inclusion criteria for the review: the population was consistent with the marketing authorisation that was subsequently granted for vamorolone and the EAG's clinical expert considered that the interventions/comparators and outcomes were appropriate for this submission. However, the EAG noted that the included study designs were RCTs (followed by single-arm extensions) and single-arm trials despite the protocol also stating that a non-RCT study design was an exclusion criterion. The EAG noted that this led to single-arm studies being both included and excluded from the SLR. Given that non-RCT data was used in the submission via the VBP15-LTE study, the EAG was concerned that other non-RCTs were potentially excluded from the SLR on an ad hoc basis.

The EAG was also unclear about the final studies included in the company's SLR reported clinical effectiveness evidence. The PRISMA diagram presented in Appendix D (Figure 1) indicated that 60 records reporting 49 studies were included in the SLR. For the clinical

effectiveness review, this included 27 papers reporting on 16 trials. The company provided a list of the 60 papers included in the overall SLR, but it was unclear which of the 60 papers were included in the clinical effectiveness review. No details were presented as to the interventions evaluated in the 16 included trials, no results from the trials were presented, and no quality assessment was presented.

The EAG considered that the methods for screening and data extraction were adequate. The tool used for the quality assessment of RCTs was reported to be the CRD's "minimum criteria for assessment of risk of bias in RCTs".[8] Single-arm studies and observational studies were reported to have been quality assessed using the Downs and Black checklist,[9] however, no quality assessment was presented in the SLR (Appendix D).

Table 5: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The company conducted SLRs for each of the research questions listed in the CS. All of the search filters required for each research question were combined into a single search, reported in Appendix D, which covered not only the clinical evidence, but also adverse effects, CEA, HRQoL, and cost and resource use. Published search filters were mostly used (except for the resource use search), and a suitably broad range of sources were searched. Further details of the search are presented in the CS. However, the EAG had concerns over the quality of the searches reported. For example, only thesaurus terms were used to describe the interventions (i.e. no free text terms were used), therefore the search may have missed articles not yet indexed, or poorly indexed. Zero search results are reported for Econlit, but when searched by PenTAG via EBSCOhost there were two relevant articles (although these were picked up via other databases in the company search). Reporting of the search was also unclear at times. For example, while only one search was reported, in the economics section, three searches at different points in time are described: "initial" [2017], "updated" [2019] and then "targeted" [no date reported]. Also, no details were provided of how supplemental searches were executed, and some numbers do not tally between the text and the PRISMA diagram (Figure 1, Appendix D).

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Inclusion criteria	Appendix D, Table 1	The population was consistent with the marketing authorisation that was subsequently granted for vamorolone. The EAG's clinical expert considered the interventions/comparators and outcomes to be appropriate for this submission. The included study designs were RCTs (including single-arm extensions) and single arm trials but the SLR protocol stated that non-RCT study design was an exclusion criteria. The EAG noted that this led to single-arm studies being both included, and excluded, from the SLR. Given data from the dose-finding safety study (VBP15-LTE) was presented in the CS and data from this study used in the economic model, the EAG was concerned that single-arm studies were potentially excluded from the SLR in a non-systematic way.
Screening	Appendix, D1.1	The EAG considered the methods for screening to be adequate.
Data extraction	Appendix, D1.1	The EAG was satisfied with the data extraction process as detailed in Appendix D.
Tool for quality assessment of included study or studies	Appendix, D1.1 and D1.3	The tool used for the quality assessment of RCTs was reported to be the CRD's "minimum criteria for assessment of risk of bias in RCTs".[8] Single-arm studies were reported to have been assessed though the Downs and Black checklist.[9] No quality assessment was presented in the SLR in Appendix D. However, quality assessment of VISION-DMD using CRD's minimum criteria was presented in Section B.2.5 of the CS.
Evidence synthesis	Appendix, D1.1	The PRISMA diagram presented in Appendix D indicated 60 records were included in the SLR. In the clinical review, 27 papers reported on 16 trials were included. Outside of the PRISMA diagram, the company did not present any details of the included clinical studies, including the interventions being tested or the outcomes reported. No evidence synthesis of clinical studies was presented.

Abbreviations: CS, Company submission; CEA, cost-effectiveness analysis; EAG, External Assessment Group; HRQoL, health-related quality of life; PenTAG, Peninsula Technology Assessment Group; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomised controlled trial; SLR, systematic literature review

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

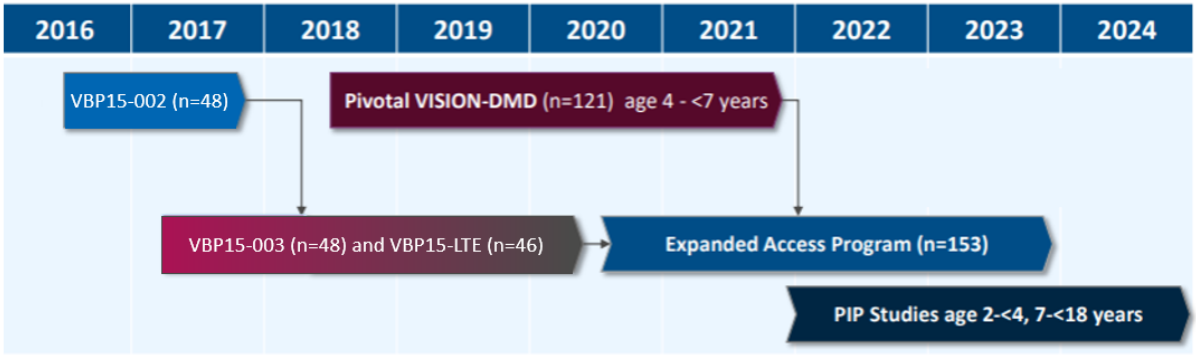
The CS described five Phase II trials of vamorolone:

- VISION-DMD[10,11]
- VBP15-002[12]
- VBP15-003[13]
- VBP15-LTE[14]
- VBP15-006 ("PIP studies")[15]

These are shown in Figure 2, below. The trial in bold was ongoing at the time of the EAG's appraisal. The participants recruited to VBP15-LTE were boys who had previously completed the VBP15-002 and VBP15-003 trials.

As noted previously, the company only presented evidence from VISION-DMD and VBP15-LTE in the CS. Moreover, the evidence presented from VBP15-LTE was limited to a subgroup of participants in the trial. The company presented methodological information about VBP-15-002 and VBP-12-003 trials in the main CS, with summary of results presented in appendices. In Section B.2.11 of the CS, the company noted that VBP15-006[15] was an ongoing, Phase II, open-label, multiple dose study to evaluate vamorolone in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD. This was referred to as "PIP Studies" (paediatric investigational plan) in Figure 2, below. No preliminary results were presented for this trial.

Figure 2: Overview of the vamorolone clinical trial program



Source: CS, Figure 4, Document B

Table 6: Clinical evidence included in the company submission

Study name and acronym	Study design	Phase	Participants enrolled	Population Population	Intervention(s)	Comparator(s)
VISION-DMD[10,11]	Double-blind RCT (24 weeks) followed by treatment extension period (20 weeks)	2b	121	Ambulatory boys aged 4 to <7 years with DMD who were glucocorticoid-naïve at study entry.	• Vamorolone 2.0 mg/kg/day • Vamorolone 6.0 mg/kg/day	• Prednisone 0.75 mg/kg/day • Placebo
VBP15-LTE[14]	Open-label trial (2 years)	2	46[b]	Boys aged 4.5 to 7.5 years with DMD who had completed VBP15-002 (2 weeks) and VBP15-003 (24 weeks) prior to joining VBP15-LTE.	Vamorolone: • 0.25 mg/kg/day • 0.75 mg/kg/day • 2.0 mg/kg/day • 6.0 mg/kg/day A participant's dose could be up-titrated to a maximum of 6.0 mg/kg/day during the trial.	NA

Abbreviations: DMD, Duchenne muscular dystrophy; kg, kilograms; mg, milligrams; NA, not applicable; RCT, Randomised controlled trial.

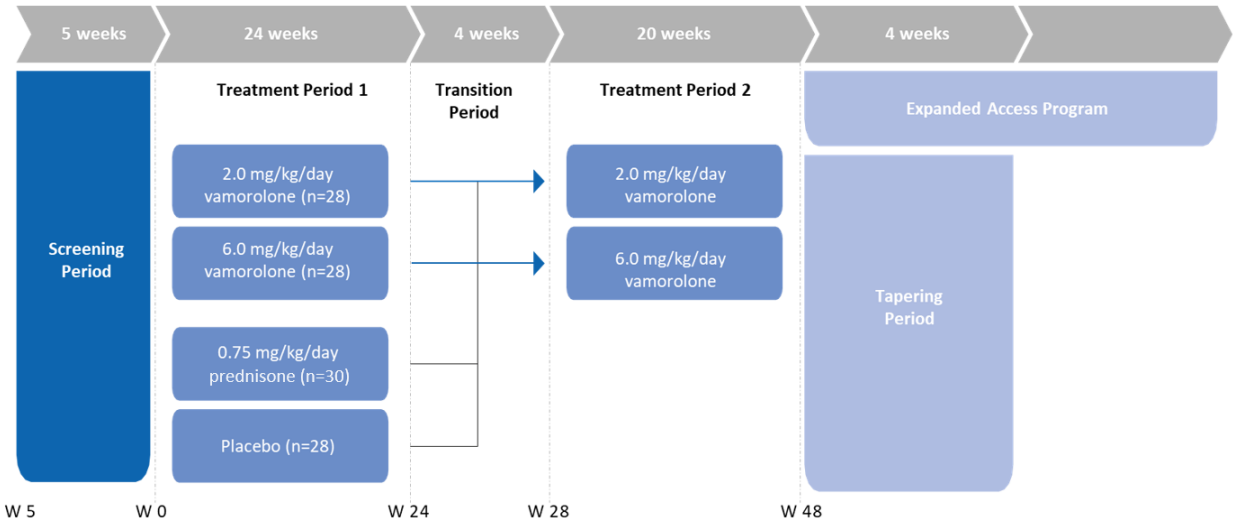
3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The pivotal trial for this submission was **VISION-DMD**,[10,11] a Phase IIb, double-blind, randomised, placebo and active-controlled 48-week trial (Figure 3). The study was undertaken at 33 centres, six of which were in the UK. The EAG was unaware of any rationale to suggest that the trial would have limited generalisability to NHS care. The trial recruited 121 ambulatory boys aged 4 to <7 years with DMD who were glucocorticoid-naïve at study entry.

In treatment period one (24 weeks), participants were randomised 1:1:1:1 to four treatment arms: vamorolone 6.0 mg/kg/day; vamorolone 2.0 mg/kg/day; prednisone 0.75 mg/kg/day; placebo. Following completion of period one, all participants entered a 4-week transition period (i.e., Week 25 to Week 28) during which vamorolone was administered at the same dose as in treatment period one, but the dose of prednisone was tapered to zero. After the transition period, participants then entered treatment period two (20 weeks), during which all participants who were previously treated with either prednisone or placebo were randomised to vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day. Participants who had received vamorolone in treatment period one continued on the vamorolone dose to which they were randomised.

Figure 3: Study design of VISION-DMD



Abbreviations: kg, kilogram; mg, milligram; n, number of participants.
Source: CS, Figure 5, Document B

Trial VBP15-LTE Was the follow-on extension for participants in studies VBP15-002 and VBP15-003. Study **VBP15-002**[12] (NCT02760264) was a Phase IIa, open-label, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys with DMD over a period of two weeks. There were 11 participating international academic clinical recruitment sites, including one site in the UK. Vamorolone was administered to a total of 48 participants at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day. Assignment to dose was not random and the method used was not clear.

Participants who completed VBP15-002 were eligible to join study **VBP15-003**[13] (NCT02760277), which was a Phase II, open-label, multicentre extension study to assess the long term safety and efficacy of vamorolone for DMD over a period of 24 weeks. Forty-eight participants joined the trial and continued on the vamorolone dose assigned at the start of VBP15-002.

Participants who completed VBP15-003 were eligible to join **VBP15-LTE**[14] (NCT03038399), a Phase II study where participants were treated and followed for 24-months. Forty-six participants joined the trial and began the study on the dose assigned at the start of VBP15-002. Their dose was then either escalated to a dose between 2.0 and 6.0 mg/kg/day or maintained between 2.0 and 6.0 mg/kg/day for the trial period. However, the company only reported on the subgroup of 23 participants who were assigned to 2.0 mg/kg/day or 6.0 mg/kg/day in VBP15-002.

3.2.2.2. Population

The population in the final scope issued by NICE was people with DMD and the population addressed in the CS was people with DMD aged 4 years and older. The participants recruited for VISION-DMD and VBP15-LTE were compatible with the scope.

Trial eligibility criteria

Eligibility criteria for VISION-DMD[10,11] were provided in the CS (Document B, Table 9). The trial recruited 121 ambulatory boys aged four to less than seven years old with DMD. This is in line with the EMA Committee for Medicinal Products for Human Use (CHMP) recommendation. The trial included a number of additional eligibility criteria, notably that participants recruited to the trial were required to be ambulatory without assistive devices, able to stand without assistance in less than 10 seconds and weighed between 13 kg and 40 kg at screening. The EAG's clinical

experts explained that children are expected to be ambulatory and able to stand without assistance in less than 10 seconds until they are at least seven years old. Therefore, they would not expect the population of the trial to be biased by these eligibility criteria. The EAG understand that few children would fall outside the weight criteria when aged four to less than seven years old. Participants were required to be glucocorticoid-naïve at study entry, which does not represent the incident population of people with DMD who have typically received one or more glucocorticoids for their DMD. The EAG was uncertain to what extent outcome data from the trials would generalise to positioning after first line (Key Issue 2).

The company did not provide detailed eligibility criteria for VBP15-002[12] in the CS. However, the EAG understood from Conklin et al. (2018)[12] that the criteria for VBP15-002 were a close match to those used for VISION-DMD. VBP15-002 enrolled 48 corticosteroid-naïve participants aged 4 to less than 7 years old with DMD. All 48 participants completed VBP15-002 and joined VBP15-003[13], of whom 46 completed treatment. The 46 participants who completed VBP15-003 joined VBP15-LTE.[14] Therefore, the children who joined VBP15-LTE were boys aged 4.5 to 7.5 years with DMD who had previous been treated with vamorolone for six months.

In sum, children included in VISION-DMD and VBP15-LTE were recently diagnosed with DMD and had either no exposure of glucocorticoids, or in the case of VBP15-LTE, had been treated for 6 months with vamorolone. The EAG understood that this did not include older people with DMD and those who had previously been treated with other glucocorticoids, prednisone/prednisolone or deflazacort, for a period of years. This population was not represented in the vamorolone trials for which results were presented in the CS.

Baseline characteristics

Clinical effectiveness outcomes with vamorolone were reported in the mITT population, who were randomised participants who had at least one dose of study medication and at least one post-baseline efficacy assessment. The demographic characteristics of the mITT population in VISION-DMD were reported in Table 10 in CS Document B. The EAG's clinical experts regarded the participants in VISION-DMD to be generalisable to people in the NHS. They noted that diagnosis in VISION-DMD used a muscle biopsy to look at dystrophy immunofluorescence. At present, diagnosis in the NHS is made on the basis of genetic testing and muscle biopsy is rarely, if ever, required. However, the EAG nevertheless considered that the participants in the trial were representative of NHS clinical practice.

VISION-DMD was a trial with four treatment arms each containing approximately 30 participants. The EAG noted variation between the vamorolone 6.0 mg/kg/day arm and the prednisone arm in four demographic characteristics reported:

- Mean (SD) time to stand from supine (TTSTAND) velocity was 0.19 (0.06) rises per second in the vamorolone 6.0 mg/kg/day arm and 0.22 (0.06) in the prednisone arm. The difference between the two treatment arms was greater than the minimally clinically important difference (MCID; >0.023 rises/sec) for TTSTAND velocity in Table 11 (taken from Table 15, Document B), meaning that those in the vamorolone 6.0 mg/kg/day arm performed poorer on this test at baseline compared to those receiving prednisone.
- The mean (SD) 6-minute walk test (6MWT) distance was 312.5 (56.19) metres in the vamorolone 6.0 mg/kg/day arm and 343.32 (55.84) in the prednisone arm. The difference between the two treatment arms at baseline was greater than the MCID (26-23 metres) in Table 11 (taken from Table 15, Document B), meaning that those in the vamorolone arm performed poorer on this test at baseline compared to those receiving prednisone.
- Time to run/walk 10m (TTRW; SD) velocity was 1.9 (0.4) metres per second in the prednisone arm and 1.6 (0.3/0.4) in the vamorolone arms. The difference between the two treatment arms was greater than the MCID (0.212 m/sec) in Table 11 (taken from Table 15, Document B), meaning that those in the vamorolone arms performed worse on this test at baseline compared to those receiving prednisone.
- North Star Ambulatory Assessment (NSAA; SD) total score was 21.16 (5.45) in the prednisone arm and 18.86 (4.07) in the vamorolone 6.0 mg/kg/day arm. The difference between the two treatment arms was equal to than the MCID (2.32 points) in Table 11 (taken from Table 15, Document B), meaning that those in the vamorolone arms performed worse on this test at baseline compared to those receiving prednisone.

Overall, this suggested that those in the vamorolone 6.0 mg/kg/day arm were likely to have more progressed disease at baseline than the prednisone arm. The EAG's clinical expert confirmed that treatment effectiveness may be reduced as the disease develops, meaning that those with more severe disease at baseline may experience smaller treatment effects in the trial. However, the EAG noted that the TTSTAND, 6MWT, TTRW, and NSAA outcomes were reported (as per standard practice) as a change from baseline and the company used baseline response as a covariate in the mixed model for repeated measures (MMRM) to adjust for

differences at baseline. Given the analysis used, the EAG were not concerned that the variation in baseline characteristics led to an underestimation of the treatment efficacy of vamorolone, but it was noted to be a risk of bias (Section 3.2.2.6).

The EAG requested prior treatments received by participants in VISION-DMD at the clarification stage (Question A7). The prior use of medications appeared well balanced between treatment arms. Three (10.7%) participants in the vamorolone 6 mg/kg/day arm and two (6.5%) participants in the prednisone arm had used glucocorticoids in what the EAG understand to be transient use for no longer than one month.

No baseline characteristics were presented for the participants entering VBP15-002, the majority of whom progressed to VBP15-003 and VBP15-LTE. The company also did not provide the trial clinical study reports (CSRs) with their submission, and so the EAG was unable to identify these independently. The company did present the baseline characteristics of 23 of the 46 participants in VBP15-LTE (Table 12, Document B). These were participants assigned to vamorolone 2.0 or 6 mg/kg/day in VBP15-002/VBP15-003 and maintained at 2 mg/kg/day or more in VBP15-LTE.

Dropouts

The company presented the CONSORT flow diagram for the treatment period one (0-24 weeks) of VISION-DMD in Section D1.2 of the CS. The company detailed the dropouts in treatment period two (24-48 weeks) when assessing the quality of the trial in Table 16 in Section B.2.5 of the CS. Discontinuation in VISION-DMD is summarised below in Table 7. There were low levels of drop out in the trial: one or two participants in each arm discontinued in the initial 24 weeks of the trial (completion rate >90% in each arm), and an additional two participants discontinued in the vamorolone 6 mg/kg/day arm between 24 and 48 weeks (overall completion rate 86.7%). The reasons for discontinuation prior to 24 weeks were provided by the company. The participant in the prednisone arm who discontinued did so due to “personality change”, which may have been related to behaviour issues commonly associated with this treatment. Two participants discontinued vamorolone 6 mg/kg/day at 24 weeks, one due to a refusal to take medication and the other was physician decision due to an eye abnormality. Two participants discontinued placebo due to physician decision and two discontinued vamorolone 2 mg/kg/day due to refusal to take medication and withdrawal to participate in another trial. No details were presented as to why two participants discontinued vamorolone 6 mg/kg/day in the 24 to 48 weeks treatment period.

Table 7: Participant discontinuation by treatment arm in VISION-DMD

	Placebo (n=30)	Prednisone 0.75 mg/kg/day (n=31)	Vamorolone 2 mg/kg/day (n=30)	Vamorolone 6 mg/kg/day (n=30)
Discontinued 0 to 24 weeks	2	1	2	2
Discontinued 24 to 48 weeks	0	0	0	2
Completed study	28	29	28	26

No participants discontinued treatment in the VBP15-002 trial, two participants discontinued during VBP15-003, and five participants discontinued during VBP15-LTE. The company noted in Section B.2.3.4 of the CS that the five withdrawals from VBP15-LTE were for reasons unrelated to the study drug. However, no reasoning for withdrawals was presented for either VBP15-003 or VBP15-LTE and the EAG was unable to critique these discontinuation data.

3.2.2.3. Intervention

In the VISION-DMD trial, vamorolone was administered in a daily dose as an oral suspension, 1.33% weight/weight (wt/wt) in the vamorolone 2.0 mg/kg/day arm and 4.0% wt/wt in the 6.0 mg/kg/day arm. Duration of exposure, in days, to vamorolone was presented in Table 32 of CS Document B (reproduced in Table 8, below). Notably, down-titration for vamorolone from 6.0 mg/kg/day to 4.0 mg/kg/day was not part of the VISION-DMD protocol and the EAG understood that participants used the dose to which they were randomised, outside of dose interruptions or discontinuations due to adverse events, until tapering occurred at the end of the trial. In Section 10.3.1.4. of the VISION-DMD CSR, the company report that 9 subjects had a total of eleven important protocol deviations. These included missed doses and incorrect doses. It was unclear from the reporting what treatment arms these errors occurred in. The EAG was not concerned that these protocol deviations would bias the effect estimates.

Table 8: Summary of 24-week exposure[a] in VISION-DMD

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Median duration of exposure, days (range)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Total exposure (person years)[c]	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Cumulative duration of exposure 20-24 weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: kg, kilograms; mg, milligrams; n, number.

Source: Reproduced from CS, Table 32, Document B

[a] Drug exposure was calculated over the interval for which study drug dispense and return data are available.

[b] Duration of exposure (days) = (date of last dose of study medication – date of first dose of study medication) + 1

[c] Person year = (sum of duration of exposure to treatment (days) over all patients) / 365.25

Permitted and prohibited concomitant medications in VISION-DMD were presented in Table 9 (CS, Document B). The permitted medications included inhaled and/or topical glucocorticoids, providing the dose was stable for the duration of the study, and hydrocortisone (or prednisone) stress dosing was permitted during an illness, injury, or surgical procedure to avoid an adrenal crisis. The EAG's clinical expert did not consider inhaled or topical glucocorticoids were treatments for DMD or that stress dosing with hydrocortisone (or prednisone) would influence the efficacy estimates for vamorolone. The concomitant medications received by participants were well balanced between treatment arms (Clarification Question A8).

With the exception noted above, oral glucocorticoids or other oral immunosuppressive agents, mineralocorticoid receptor agents, idebenone, medications indicated for the treatment of DMD, including Exondys51 and Translarna, were not permitted during the trial.

Interventions trialled in VBP15-002, VBP15-003 and VBP15-LTE were four doses of vamorolone: 0.25 mg/kg/day, 0.75 mg/kg/day, 2 mg/kg/day, and 6 mg/kg/day. Twelve participants were assigned to each dose in VBP15-002, this dose was maintained during VBP15-003. Participants who joined VBP15-LTE started the study on the dose they were assigned in VBP15-002 and participants who started on the 0.25 mg/kg/day or 0.75 mg/kg/day doses were then up-titrated to a dose between 2 mg/kg/day and 6 mg/kg/day until the end of follow-up. Dose de-escalations were allowed in case of intolerability. However, the company did not report the results of the participants in the 0.25 mg/kg/day or 0.75 mg/kg/day arms. The company noted that these participants had more progressed disease at six months before their dose was adjusted to between 2 mg/kg/day and 6 mg/kg/day. The company did not detail the concomitant medications used during the trials. However, the medications permitted and

prohibited during the trials were identical those in the pivotal VISION-DMD trial and the specific concomitant medications used in VISION-DMD were not a cause for concern to the EAG.

3.2.2.4. Comparator

During the first 24 weeks of VISION-DMD, treatment with vamorolone was compared to either prednisone 0.75 mg/kg/day or placebo. Duration of exposure, in days, to prednisone and placebo was presented in Table 32 of Document B and is reproduced in Table 8, above. No other trial phases or studies included a comparator arm to vamorolone. A discussion of background treatments received in the control arm can be found above in the Intervention section (3.2.2.3).

3.2.2.5. Outcomes

For the VISION-DMD trial, the company reported outcomes for all four treatment arms following treatment period one (24-week follow-up). Data after treatment period two (52 weeks) was reported for those who were originally randomised to vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day and those who switched from prednisone or placebo to vamorolone. The company also reported outcomes from the VBP15-LTE at 30 months. The company did not report all of the comparative data in the CS, but the EAG received notable missing data at clarification. For clarity, the treatments assessed in each trial are listed below.

VISION-DMD treatment period 1 (24 weeks):

- Vamorolone 6.0 mg/kg/day for 24 weeks (n=30);
- Vamorolone 2.0 mg/kg/day for 24 weeks (n=30);
- Prednisone 0.75 mg/kg/day for 24 weeks (n=31);
- Placebo for 24 weeks (n=30).

VISION-DMD treatment period 2 (48 weeks):

- Vamorolone 6.0 mg/kg/day for 48 weeks (n=28);
- Vamorolone 2.0 mg/kg/day for 48 weeks (n=38);
- Prednisone 0.75 mg/kg/day for 24 weeks followed by vamorolone 6.0 mg/kg/day for 24 weeks (n=15);

- Prednisone 0.75 mg/kg/day for 24 weeks followed by vamorolone 2.0 mg/kg/day for 24 weeks (n=15);
- Placebo for 24 weeks followed by vamorolone 6.0 mg/kg/day for 24 weeks (n=14);
- Placebo for 24 weeks followed by vamorolone 2.0 mg/kg/day for 24 weeks (n=14).

VBP15-LTE: Change scores reported from the end of VBP15-003, after six months of treatment, until the end of treatment in VBP15-LTE (30 months):

- Vamorolone 2.0 to 6.0 mg/kg/day for 30 months (n=24).

Multiple dose escalations to the highest dose (i.e., 6.0 mg/kg/d) were permitted in the LTE protocol and de-escalations were also allowed in case of intolerability, at the discretion of investigators.

The outcomes assessed in each trial phase and reported in the CS (or during clarification) are shown in Table 9.

Table 9: Clinical effectiveness outcomes from trials of vamorolone reported in the CS

Outcomes listed in the NICE scope	**VISION-DMD Phase 1 (24 weeks){Guglieri, 2022 #5}**	**VISION DMD Phase 1 and 2 (48 weeks){Hoffman, 2023 #7}**	**VBP15-LTE{Mah, 2022 #11}**
Walking ability (ambulation)	✓ 6MWT, TTRW velocity, TTSTAND velocity, TTCLIMB velocity, NSAA score	✓ 6MWT, TTRW velocity, TTSTAND velocity, TTCLIMB velocity, NSAA	✓ 6MWT, TTRW velocity, TTSTAND velocity, TTCLIMB velocity, NSAA, PODCI transfer and basic mobility
Muscle function	✓ As assessed through functional measures, above	✓ As assessed through functional measures, above	✓ As assessed through functional measures, above
Muscle strength	✓ Knee extension and elbow flexor muscle strength	×	×
Ability to undertake activities of daily living	×	×	×

Outcomes listed in the NICE scope	VISION-DMD Phase 1 (24 weeks){Guglieri, 2022 #5}	VISION DMD Phase 1 and 2 (48 weeks){Hoffman, 2023 #7}	VBP15-LTE{Mah, 2022 #11}
Bone function	✓ Height Z-score, lumbar Spine BMD and BMC, and fractures	✓ Height Z-score	✓ Height percentile
Cardiac function	×	×	×
Concordance and optimisation of treatment	×	×	×
Endocrine function	×	×	×
Lung function	×	×	×
Time to wheelchair	×	×	×
Number of falls	×	×	×
Time to scoliosis	×	×	×
Upper body function	×	×	✓ PODCI upper extremity and physical function (n=18)
Mortality	✓	✓	✓
Adverse effects of treatment	✓	✓	✓
Health-related quality of life for patients	× HRQoL was measured using PODCI and PARS III but results were not reported in the CS	×	×
Health-related quality of life for carers	×	×	×
Additional outcomes	✓ TSQM (treatment satisfaction)	×	×

Abbreviations: 6MWT, six-minute walking test; BMC, bone mineral content; BMD, bone mineral density; HRQoL, health-related quality of life; NSAA, North Star Ambulatory Assessment; PARS III, Psychosocial Adjustment and Role Skills Scale III; PODCI, Paediatric Outcomes Data Collection Instrument; TSQM, Treatment Satisfaction Questionnaire; TTCLIMB, Time to climb 4 stairs; TTRW, Time to run/walk 10m; TTSTAND, Time to stand from supine.

Overall, outcome measures reported in the CS were related to participants' ambulatory function and adverse effects of treatment. Measures of ambulatory function reported were widely accepted measures and the company defined thresholds for where change in the outcomes was known to have a clinically meaningful benefit to participants. However, the EAG nevertheless considered there to be an absence of evidence for many of the outcomes in the NICE scope, particularly aspects of the disease other than ambulatory function and outcomes that would

assess the impact of treatments on patient functioning, quality of life, and mental wellbeing. Clinical expert advice to the EAG was that some outcomes, such as cardiac function, lung function, time to scoliosis, time to wheelchair, and number of falls may not be relevant to people with DMD until later in the disease course. As those in VISION-DMD were glucocorticoid-naïve at baseline and follow-up was <12 months, the trial evidence available for vamorolone would be unable to provide an insight into the long term effects of treatment or the effects of treatment for those later in the disease course.

Details of the statistical analysis used for the VISION-DMD trial are reported in Table 14 in Document B. The primary and secondary endpoints were: time to stand from supine (TTSTAND) velocity; time to run or walk 10 metres (TTRW) velocity; time to climb four stairs (TTCLIMB) velocity; North Star Ambulatory Assessment (NSAA) score; knee extension and elbow extension muscle strength. It was notable that NSAA is a 17-item scale that grades performance of various functional skills on a scale from 0 (unable), 1 (completes independently but with modifications), and 2 (completed without compensation). The NSAA score includes, within the 17 items, rise from the floor, climbing on a box, and the ability to walk or run. These items are closely associated with other outcomes collected in the trial such as TTSTAND velocity, TTRW, and TTCLIMB velocity. However, unlike the related outcomes in this trial, it is not scored based on the time taken to complete these tasks and is rather an assessment of how they are performed.

The company conducted two different analyses of primary and secondary outcomes to account for missing data in the trial. The first analysis, conducted for the Food and Drug Administration (FDA), applied a MMRM approach using observed cases (without multiple imputation) and importantly, the MMRM included the baseline response as a covariate. The second analysis, conducted for the European Medicines Agency (EMA), did use multiple imputation using both missing at random (MAR) and missing not at random (MNAR) assumptions. The EMA analysis used Copy-Reference imputation for missing data not related to COVID-19. The primary and secondary endpoints for the vamorolone (either dose) versus prednisone comparisons used the FDA approach. The EAG considered the FDA approach to be more robust as it did not utilise the MAR assumption and used observed cases in the analysis. The EAG noted that population characteristics in VISION-DMD indicated an imbalance in characteristics suggesting that those participants in the vamorolone 6 mg/kg/day arm had more progressed disease, however the company adjusted for this imbalance by including baseline outcome data as a covariate in the MMRM.

Three patient reported outcome measures (PROMs) were collected during VISION-DMD: Paediatric Outcomes Data Collection Instrument (PODCI); Treatment Satisfaction Questionnaire (TSQM); Psychosocial Adjustment and Role Skills Scale III (PARS III). Powell et al. (2020)[16] also assessed PODCI alongside EQ-5D-3L. Powell et al. reported that most instruments, including EQ-5D-3L and PODCI, demonstrated low quality evidence and unsatisfactory or inconsistent validity in DMD, with the majority not featuring direct validation studies in this population. Powell et al. concluded that only KIDSCREEN[17,18] received an adequate rating for instrument design and a satisfactory result for content validity based on its development, yet, like the majority of PROMs, the measure had not been directly validated for use in children with DMD.

The other PROMs collected during VISION-DMD were not measures of a person's QoL. The TSQM is a measure of person's satisfaction with medication. The PARS III instrument was developed to measure psychosocial adjustment in children with chronic physical illnesses. It has been validated for this purpose in the DMD population[19] but does not extend to measure other QoL domains. The EAG did not consider the PROMs collected during VISION-DMD to be adequate measures of quality of life in children with DMD. However, the EAG was not aware of any PROMs designed to measure the quality of life (QoL) of children with DMD.

The statistical analysis used for the outcomes reported from the participants in the VBP15-002, VBP15-003 and VBP15-LTE trials was not detailed in the company submission. However, the appendix to the VBP15-LTE publication stated that the only the observed data was utilised, i.e., no multiple imputation was used.[14]

3.2.2.6. Critical appraisal of the design of the studies

The company stated that quality assessment was undertaken with appropriate checklists on studies included in the SLR. However, no quality assessment was presented in the SLR in Appendix D. In Document B, a quality assessment was presented for the pivotal trial, VISION-DMD. No quality assessment was presented for the VBP15-002/VBP15-003/VBP15-LTE trials of vamorolone.

Quality assessment of VISION-DMD

The company presented a quality assessment of the pivotal trial, VISION-DMD, in Table 16 (Section B.2.5). This assessment was conducted using the "minimum criteria for assessment of risk of bias in RCTs" set out in CRD's guidance for undertaking reviews in health care.[8] The

company undertook the assessment and concluded that VISION-DMD was a high quality study with minimal risk of bias. This has been reproduced in Table 10 with the EAG's critique of the assessment. Overall, the EAG agreed with the company that randomisation appeared to be carried out appropriately, concealment of treatment allocation was adequate, and care providers, participants and outcome assessors were blinded to treatment allocation. However, as noted in Section 3.2.2.2, the treatment arms were quite different at outset in terms of prognostic factors. The vamorolone 6 mg/kg/day arm had lower TTSTAND velocity, 6MWT distance, TTRW velocity, and NSAA total score at baseline than the prednisone arm, indicating more progressed disease. The EAG did not consider this an indication that the allocation sequence was not random, but a consequence of having too few people randomised per arm leading to treatment groups that were noticeably mismatched at baseline.

The EAG understood that there were relevant outcomes collected in the trial that were not presented in the CS. The following outcomes of the key comparison vamorolone 6.0 mg/kg/day versus prednisone at 24 weeks, were not presented in the CS but were provided at the clarification stage: TTRW velocity, NSAA score, knee extension muscle strength, and elbow flexor muscle strength. In Section B.2.6.1.9 the company presented an incomplete summary of the three PROMs collected was at 24 weeks. This summary did not detail the results for the vamorolone 6.0 mg/kg/day versus prednisone comparison.

The company collected efficacy outcomes at 48 weeks across six treatment arms, all of which were using either 6.0 or 2.0 mg/kg/day vamorolone during the 24–48 week treatment period. The outcomes in the prednisone arm who changed to vamorolone treatment were presented only in charts limiting any further analysis by the EAG. Results of the three PROMs were not reported and change in body mass index (BMI) and bone biomarkers were reported in text and this offered an incomplete summary of the results.

Overall, the EAG considered the trial to be at a moderate risk of due to selective reporting of the outcomes collected.

Table 10: EAG critique of the quality assessment of VISION-DMD

Questions	Assessment presented in the CS	EAG's critique
Was randomisation carried out appropriately?	Yes: Patients were randomised 1:1:1:1 ratio by an IXRS after patients were confirmed to have met all study entry criteria, at least 10 days prior to the	The EAG agreed with the company's assessment

Questions	Assessment presented in the CS	EAG's critique
	Baseline Day -1 Visit). Patients were stratified by age at study entry (<6 years and ≥6 years).	
Was the concealment of treatment allocation adequate?	Yes. To maintain the double-blind in this period 1, all patients received either a matching placebo for vamorolone (i.e., a placebo oral suspension), a matching placebo for prednisone (i.e., a placebo tablet) or both (i.e., placebo oral suspension and placebo tablet). Maintenance of the blind was aided by use of amber bottles and acceptability for taste for both the vamorolone and placebo suspensions.	The EAG agreed with the company's assessment
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes: There was no significant difference in the baseline characteristics reported between the treatment arms.	As noted in Section 3.2.2.2, the EAG considered the arms were quite different at outset in terms of baseline characteristics/ prognostic factors. However, MMRM the analysis adjusted for baseline values.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes: Investigators, study site staff, patient's parent/legal guardian, patient, and study monitors were unaware of the treatment assignment throughout the duration of the study.	The EAG agreed with the company's assessment
Were there any unexpected imbalances in dropouts between groups?	No: There were no unexpected imbalances in dropouts between groups. Withdrawals by patients were similar in all arms up to Week 24 (prednisone, n=1; placebo, n=2; vamorolone 2.0 mg/kg/day, n=2; vamorolone 6.0 mg/kg/day, n=2) and up to Week 48 (prednisone, n=1; placebo, n=2; vamorolone 2.0 mg/kg/day, n=2; vamorolone 6.0 mg/kg/day, n=4).	The EAG agreed with the company's assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No: No evidence to suggest that the authors measured more outcomes than they reported.	There were relevant outcomes collected in the trial that were not presented. Four outcomes linked to the vamorolone 6.0 mg/kg/day versus prednisone comparison were presented after a request from

Questions	Assessment presented in the CS	EAG's critique
		the EAG at the clarification stage. Reporting of PROMs collected was incomplete at either 24 or 48 weeks. Outcomes from the prednisone to vamorolone 6.0 mg/kg/day arm at 48 weeks were reported only in charts while results in the vamorolone to vamorolone arms at 48 weeks were provided in tables.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes: Efficacy analysis was performed using the mITT-1 population for efficacy at Week 24 and using the mITT-2 population for efficacy at Week 48. Following the Intent-to-Treat principle, patients were analysed according to the treatments and strata to which they were assigned at randomisation.	The EAG agreed with the company's assessment

Abbreviations: AE, adverse events; EAG, External Assessment Group; IXRS, Interactive voice/web Response System; mITT, modified intention to treat; n, number.

Quality assessment of VBP15-002, VBP15-003, and VBP15-LTE trials

No quality assessment was presented for the VBP15-002,[12] VBP15-003[13], and VBP15-LTE trials.[14] These were consecutive trials where people who completed VBP15-002 were eligible to join VBP15-003, and people who completed VBP15-003 were eligible to join VBP15-LTE. Therefore, the EAG offers a comment on the potential risks of bias pertaining to all three trials.

As open-label, uncontrolled studies, these studies are at an increased risk of bias as it is not possible to determine to what extent changes in the outcomes are due to reasons other than the treatment, and some types of outcomes can be influenced by knowledge of the treatment being received. The trial eligibility criteria of VBP15-002 were closely matched to VISION-DMD and the population was relevant to the appraisal and matched the population in the final scope issued by NICE. However, it was unclear how participants were assigned to treatment arms using vamorolone (at 0.25, 0.75, 2.0, or 6.0 mg/kg/day). Data were only reported in the CS for a subgroup of 23 (50%) of participants in VBP15-LTE who used vamorolone between 2.0 and 6.0 mg/kg/day from the start of VBP15-002.

3.2.3. Description and critique of the results of the studies

In this section, the EAG report the efficacy and safety results submitted by the company from the VISION-DMD TRIAL and the VBP15-LTE study. In this section, the EAG refer to minimal clinically important different (MCID) thresholds reported by the company in Table 15 in Document B and reproduced below in Table 11. The minimum MCID represents the smallest improvement in the outcome that has a meaningful benefit for the person and can represent a standard for determining effectiveness and patient satisfaction with a treatment. The company did not present MCIDs for the exploratory endpoints, knee extension and elbow flexor muscle strength. Within the timeframe of its appraisal, the EAG was unable to validate the MCIDs provided by the company or identify MCIDs for other outcomes.

Table 11: Minimal clinically important different (MCID) thresholds

Endpoint	MCID
TTSTAND velocity	>0.023 rises/sec
6MWT	>26-32 metres
TTRW velocity	>0.212 m/sec
TTCLIMB velocity	>0.035 task/sec
NSAA	>2.32 points

Abbreviations: 6MWT, Six-minute walk test; NSAA, North Star Ambulatory Assessment; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine

Source: adapted from CS, Table 15, Document B

The EAG has divided up the description and critique of the results of the studies into the following three sections:

- VBP15-LTE clinical effectiveness results
- VBP15-LTE clinical effectiveness results : outcomes following 48 weeks of vamorolone and outcomes following 24 weeks of either prednisone or placebo followed by 24 weeks of vamorolone
- VBP15-LTE clinical effectiveness results : outcomes following 30 months of vamorolone at varying doses between 2.0 to 6.0 mg/kg/day

3.2.3.1. VISION-DMD clinical effectiveness results: vamorolone versus prednisone at 24 weeks

A limited selection of efficacy outcome results comparing vamorolone at 6.0 or 2.0 mg/kg/day with prednisone were presented in the CS. The company provided the missing outcome data at the clarification stage (Question A2).

TTSTAND velocity

Participants in all treatment arms, excluding placebo, showed a clinically meaningful improvement in the time taken to stand from supine (TTSTAND) after 24 weeks. Standard errors showed that the treatment effect varied across participants, which is consistent with clinical advice to the EAG that there is variation in response to steroids across people with DMD.

Least squares means (LSM; SE) TTSTAND velocity was numerically faster in the prednisone arm than the vamorolone 2.0 and 6.0 mg/kg/day arms. The effect approached statistical significance as compared with the 2.0 mg/kg/day arm (Table 12). The benefit in the prednisone arm versus the vamorolone 6.0 mg/kg/day arm was close to the MCID for TTSTAND velocity (>0.023 rises/sec). The benefit in the prednisone arm versus the vamorolone 2.0 mg/kg/day arm was greater than the MCID. Vamorolone at either 2.0 or 6.0 mg/kg/day was more efficacious than placebo (effect statistically significant and greater than the MCID).

Overall, the results suggested that vamorolone at either dose offered a meaningful clinical benefit to participants over and above placebo, but that those receiving prednisone were faster to stand than those receiving vamorolone. While this effect was not statistically significant, it matched or exceeded the MCID for this outcome, and the EAG considered that the lack of statistical significance was plausibly related to the sample size and variability in the treatment response across participants in all treatment arms, rather than the absence of an effect.

Table 12: TTSTAND velocity change from baseline to Week 24: vamorolone versus prednisone/placebo

rises/sec	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	0.20 (0.06)	0.22 (0.06)	0.18 (0.05)	0.19 (0.06)
Week 24, mean (SD)	0.19 (0.09)	0.29 (0.09)	0.23 (0.09)	0.24 (0.08)

rises/sec	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Change from baseline at Week 24, mean (SD)	-0.01 (0.06)	0.07 (0.07)	0.04 (0.09)	0.05 (0.07)
LSM (SE) change from baseline	-0.01 (0.01)	0.07 (0.01)	0.03 (0.01)	0.05 (0.01)
LSM difference (SE) vs prednisone	NR	NA	-0.03 (0.02)	-0.02 (0.02)
95% CI vs prednisone	NR	NA	-0.07, 0.00	-0.06, 0.02
p-value vs prednisone	NR	NA	0.0588	0.2976
LSM difference (SE) vs placebo	NA	NR	0.05	0.06 (0.02)
95% CI vs placebo	NA	NR	0.01, 0.08	0.02, 0.10
p-value vs placebo	NA	NR	0.0171	0.002

Abbreviations: CI, confidence interval; kg, kilograms; LSM, least squares mean; mg, milligrams; n, number; NA, not applicable; NR, not reported; SE, standard error.

6MWT distance

Results of the 6-minute walking test (6MWT) showed that participants in all treatment arms, except placebo, showed a clinically meaningful improvement in the outcome after 24 weeks of treatment. As with TTSTAND, measures of variation suggested that the effect was varied across the sample, meaning that some but not all participants may have benefitted from treatment.

LSM (SE) 6MWT distance was numercially better in the prednisone arm than in either of the vamorolone dose arms: during the six minutes, people who received prednisone were able to walk a LSM (SE) of 48.23 (9.12) metres further compared to 28.34 (9.56) metres and 23.88 (9.69) metres in the vamorolone at 6.0 or 2.0 mg/kg/day arms respectively. However, the difference did not exceed the MCID (>26-32 metres), meaning that the relative improvement after predinisone would not have an overall meaningful impact on participants' lives (Table 11). Vamorolone at either 2.0 or 6.0 mg/kg/day was more efficacious than placebo (effect statistically significant and greater than the MCID).

Table 13: 6MWT distance change from baseline to Week 24: vamorolone versus prednisone/placebo

metres	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	354.5 (77.59)	343.3 (55.84)	316.1 (58.43)	312.5 (56.19)
Week 24, mean (SD)	339.0 (60.90)	395.5 (57.32)	349.1 (65.99)	355.9 (50.92)
Change from baseline at Week 24, mean (SD)	-23.9 (59.62)	39.7 (30.620	31.0 (51.12)	28.8 (49.66)
LSM (SE) change from baseline	-13.25 (10.04)	48.23 (9.12)	23.88 (9.69)	28.34 (9.56)
LSM difference (SE) vs prednisone	NR	NA	-24.35 (13.21)	-19.89 (13.10)
95% CI vs prednisone	NR	NA	-50.61, 1.91	-45.93, 6.15
p-value vs prednisone	NR	NA	0.0687	0.1326
LSM difference (SE) vs placebo	NA	NR	37.12 (13.87)	41.59 (13.76)
95% CI vs placebo	NA	NR	9.55, 64.70	14.23, 68.94
p-value vs placebo	NA	NR	0.0089	0.0033

Abbreviations: CI, confidence interval; kg, kilograms; LSM, least squares mean; mg, milligrams; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

TTRW velocity

Participants in the prednisone and vamorolone 6.0mg/kg/day arms showed an improvement in the time needed to run/walk 10 metres (TTRW) after 24 weeks' of treatment, but those in the vamorolone 2.0 mg/kg/day and placebo arms did not. As with previous outcomes, measures of variability indicated that the response varied across participants.

LSM (SE) TTRW velocity was numerically faster in the prednisone arm than the vamorolone 6.0 mg/kg/day arm and statistically significantly faster than the vamorolone 2.0 mg/kg/day arm (Table 14). The LSM (SE) velocity in the prednisone arm improved by 0.37 (0.05) metres per second (m/sec) compared to 0.26 (0.05) m/sec and 0.14 (0.06) m/sec in the vamorolone at 6.0 or 2.0 mg/kg/day arms respectively. The benefit in the prednisone arm versus the vamorolone

2.0 mg/kg/day arm was greater than the MCID (>0.212 m/sec). The benefit of vamorolone 6.0 mg/kg/day over placebo was both statistically significant and greater than the MCID.

Overall, the results showed that prednisone was more effective than vamorolone 2.0 mg/kg/day but not meaningfully different than vamorolone 6.0 mg/kg/day. Vamorolone was more effiective than placebo at a dose of 6.0 g/kg/day but not at 2.0 mg/kg/day.

Table 14: TTRW velocity change from baseline to Week 24: vamorolone versus prednisone/placebo

metres/sec	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	1.74 (0.35)	1.90 (0.43)	1.56 (0.29)	1.60 (0.36)
Week 24, mean (SD)	1.77 (0.44)	2.25 (0.43)	1.72 (0.37)	1.89 (0.41)
Change from baseline at Week 24, mean (SD)	0.02 (0.33)	0.34 (0.24)	0.16 (0.23)	0.28 (0.28)
LSM (SE) change from baseline	0.01 (0.06)	0.37 (0.05)	0.14 (0.06)	0.26 (0.05)
LSM difference (SE) vs prednisone	NR	NA	-0.23 (0.08)	-0.11 (0.08)
95% CI vs prednisone	NR	NA	-0.38, -0.08	-0.26, 0.04
p-value vs prednisone	NR	NA	0.0036	0.1381
LSM difference (SE) vs placebo	NA	NR	0.13 (0.08)	0.24 (0.08)
95% CI vs placebo	NA	NR	-0.03, 0.28	0.09, 0.39
p-value vs placebo	NA	NR	0.10	0.00

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

TTCLIMB velocity

Results showed that participants in all treatment arms, except placebo, had a clinically meaningful improvement in the time needed to climb four stairs (TTCLIMB) after 24 weeks of treatment.

LSM (SE) TTCLIMB velocity was statistically significantly faster in the prednisone arm than in either of the vamorolone arms (Table 15). In the prednisone arm, velocity increased by 0.11 (0.10) steps per second (step/sec) compared to 0.06 (0.01) step/sec and 0.05 (0.08) step/sec in the vamorolone arm at 6.0 or 2.0 mg/kg/day arms, respectively. In both cases the benefit in the prednisone arm over the vamorolone dose arms was greater than the MCID (>0.035 task/sec) reported in Table 11.

Overall, prednisone was more effective than vamorolone at either 2.0 or 6.0 mg/kg/day. Vamorolone was more efficacious than placebo at either dose (effect statistically significant and greater than the MCID).

Table 15: TTCLIMB velocity change from baseline to Week 24: vamorolone versus prednisone/placebo

step/sec	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	0.25 (0.09)	0.29 (0.11)	0.20 (0.05)	0.21 (0.09)
Week 24, mean (SD)	0.25 (0.12)	0.41 (0.16)	0.26 (0.08)	0.27 (0.10)
Change from baseline at Week 24, mean (SD)	-0.01 (0.05)	0.11 (0.10)	0.06 (0.06)	0.07 (0.06)
LSM (SE) change from baseline	-0.01 (0.02)	0.11 (0.01)	0.05 (0.02)	0.06 (0.01)
LSM difference (SE) vs prednisone	NR	NA	-0.06 (0.02)	-0.05 (0.02)
95% CI vs prednisone	NR	NA	-0.10, -0.02	-0.09, -0.01
p-value vs prednisone	NR	NA	0.0057	0.0193
LSM difference (SE) vs placebo	NA	NR	0.06 (0.02)	0.07 (0.02)
95% CI vs placebo	NA	NR	0.02, 0.1	0.03, 0.11
p-value vs placebo	NA	NR	0.0056	0.0008

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

NSAA score

Results showed that participants in all treatment arms, except placebo, showed a clinically meaningful improvement in functional skills as assessed by the NSAA scale after 24 weeks of treatment. People receive a score between 0 to 34, where a higher score is considered better. Measures of variability suggested some variation in response across participants. LSM (SE) NSAA score was numercially higher in the prednisone arm than in either of the vamorolone dose arms (Table 16). The LSM (SE) change from baseline was 4.5 (3.66) points in the prednisone arm compared to 2.85 (0.61) points and 2.52 (0.86) step/sec in the vamorolone at 6.0 or 2.0 mg/kg/day arms respectively. In neither case was the benefit in the prednisone arm over the vamorolome arms greater than the MCID (>2.32 points) reported in Table 11.

Overall, prednisone had a numerical but not a clinically meaninful benefit over vamorolone at either dose. Vamorolone was more efficacious than placebo at either dose (effect statistically significant and greater than the MCID).

Table 16: NSAA score[a] change from baseline to Week 24: vamorolone versus prednisone

	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	18.9 (5.30)	21.2 (5.45)	17.2 (4.66)	18.9 (4.07)
Week 24, mean (SD)	18.9 (5.60)	25.6 (5.47)	20.4 (5.62)	22.0 (5.17)
Change from baseline at Week 24, mean (SD)	-0.2 (2.57)	4.5 (3.66)	3.0 (3.11)	3.2 (3.18)
LSM (SE) change from baseline	-0.73 (0.62)	4.29 (0.60)	2.52 (0.63)	2.85 (0.61)
LSM difference (SE) vs prednisone	NR	NA	-1.76 (0.86)	-1.44 (0.83)
95% CI vs prednisone	NR	NA	-3.48, -0.05	-3.09, 0.20
p-value vs prednisone	NR	NA	0.0437	0.0848
LSM difference (SE) vs placebo	NA	NR	3.25 (0.87)	3.57 (0.84)
95% CI vs placebo	NA	NR	1.53, 4.97	1.90, 5.25
p-value vs placebo	NA	NR	0.0003	<0.0001

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

Note: [a] Range of scores is 0-34. Higher is better.

Knee extension and elbow flexor muscle strength

Participants in all arms, including those receiving placebo, showed an improvement in knee extension muscle strength after 24 weeks of treatment. As noted previously, the EAG were not aware of a MCID for this outcome to determine whether these differences would have been clinically meaningful for participants. Measures of variation suggested that there was variability in response across participants.

LSM (SE) knee extension muscle strength was numerically greater in the prednisone arm than the vamorolone 6.0 mg/kg/day arm, and statistically significantly greater than the vamorolone 2.0 mg/kg/day arm (Table 17). Vamorolone at either 2.0 or 6.0 mg/kg/day offered a numerical benefit over placebo.

Table 17: Knee extension muscle strength change from baseline to Week 24: vamorolone versus prednisone

	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline (kg), mean (SD)	5.57 (2.04)	6.13 (1.41)	5.30 (1.81)	5.47 (1.74)
Week 24, mean (SD)	5.64 (2.37)	6.89 (1.86)	5.37 (2.15)	5.52 (2.22)
Change from baseline at Week 24, mean (SD)	0.15 (2.10)	0.85 (1.57)	0.12 (1.32)	0.28 (1.93)
LSM (SE) change from baseline	-0.06 (0.36)	1.01 (0.34)	0.00 (0.38)	0.01 (0.36)
LSM difference (SE) vs prednisone	NR	NA	-1.01 (0.50)	-0.91 (0.48)
95% CI vs prednisone	NR	NA	-2.00, -0.02	-1.87, 0.05
p-value vs prednisone	NR	NA	0.0456	0.0617
LSM difference (SE) vs placebo	NA	NR	0.07 (0.51)	0.16 (0.49)
95% CI vs placebo	NA	NR	-0.95, 1.08	-0.82, 1.14
p-value vs placebo	NA	NR	0.8987	0.7411

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

Participants in all treatment arms, except placebo, showed an imrpovement in muscle strength after 24 weeks of treatment. The EAG did not have a MCID for this outcome to appraise whether this change would have been clinically meaningful to participants. Measures of variation suggested that there was variability in treatment response across participants.

Counterintuitively, elbow flexor muscle strength improved more (numerically) following the lower 2.0 mg/kg/day dose of vamorolone than the 6.0 mg/kg/day dose. LSM (SE) elbow flexor muscle strength was statistically significantly greater in the prednisone arm than the vamorolone 6.0 mg/kg/day arm, and the prednisone arm was numerically greater than the vamorolone 2.0 mg/kg/day arm (Table 18).

Overall, prednisone was the most effective treatment for elbow muscle strength, though vamorolone showed some benefits over placebo.

Table 18: Elbow flexor muscle strength change from baseline to Week 24: vamorolone versus prednisone

	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline (kg), mean (SD)	3.38 (1.49)	3.27 (0.94)	2.68 (0.81)	2.86 (0.78)
Week 24, mean (SD)	3.26 (1.33)	4.11 (0.98)	3.48 (0.94)	3.34 (1.13)
Change from baseline at Week 24, mean (SD)	-0.15 (1.41)	0.86 (0.78)	0.74 (1.23)	0.50 (1.16)
LSM (SE) change from baseline	0.02 (0.21)	1.05 (0.19)	0.61 (0.22)	0.43 (0.20)
LSM difference (SE) vs prednisone	NR	NA	-0.44 (0.29)	-0.61 (0.27)
95% CI vs prednisone	NR	NA	-1.02, 0.14	-1.16, -0.07
p-value vs prednisone	NR	NA	0.1353	0.0269
LSM difference (SE) vs placebo	NA	NR	0.59 (0.30)	0.41 (0.28)
95% CI vs placebo	NA	NR	-0.01, 1.19	-0.15, 0.98
p-value vs placebo	NA	NR	0.0546	0.1485

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

Health-related quality of life/ patient reported outcomes

The company did not report the results from the PROMs assessed during the trial (PODCI, PARS III and TSQM). In Section B.2.6.1.9 of the CS, the company stated that results for both the PODCI and the TSQM showed no statistically significant differences between either vamorolone doses and placebo, and vamorolone 2.0 mg/kg/day showed better adjustment for anxiety and depression compared with prednisone as assessed by PARS III. The EAG assumed that no treatment benefit as assessed using PARS III was identified for the higher dose of vamorolone as compared to other treatment arms. As the company did not present these data, the EAG was unable to appraise the reliability of the company's statements.

Subgroup analyses

At clarification (Question A6), the company provided subgroup analyses to compare the treatment effect of vamorolone 6.0 mg/kg/day versus prednisone on the TTSTAND velocity outcome across different population subgroups. A forest plot of subgroup treatment effects has been reproduced in Figure 4, below.

Overall, relative treatment effects between vamorolone and prednisone were fairly consistent across subgroups tested. In all cases, however, 95% confidence intervals were wide, suggesting that there is uncertainty in all treatment effects. This was not surprising, given the small sample size of the trial meaning that subgroup analyses may be underpowered. There was some evidence that the treatment effect may vary according to participants ethnicity and age, but the EAG was not confident in these findings given the uncertainty in treatment effects.

In addition, the company presented subgroup analysis for the vamorolone 6.0 mg/kg/day versus placebo comparison using the TTSTAND velocity outcome in Figure 17 in Section B.2.7 of the CS. This indicated a consistent benefit of vamorolone 6.0 mg/kg/day over placebo across the subgroup categories.

Figure 4: Forest plot TTSTAND velocity in subgroups: vamorolone 6 mg/kg/day versus prednisone

Abbreviations: 6MWT, Six-minute walk test; BL, baseline; kg, kilograms; mg, milligrams; mITT, modified intention to treat; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine.

3.2.3.2. VISION-DMD clinical effectiveness results at 48 weeks

In Section B.2.6.2, the company presented four selected efficacy outcomes in VISION-DMD participants who had received 48 weeks of treatment with vamorolone. The company also presented some efficacy data in participants who had 24 weeks of treatment with prednisone followed by 24 weeks of treatment with vamorolone 6.0 mg/kg/day.

48-week treatment with vamorolone

Improvements in TTSTAND velocity, 6MWT distance, TTRW velocity, and NSAA score demonstrated at 24 weeks in participants treated with vamorolone were largely maintained after 48 weeks of treatment (Table 19). There was no consistent evidence of an improvement or decline in treatment effect in the vamorolone 6.0 mg/kg/day arm, though there was a trend for a decline in the treatment effect in those treated with 2.0 mg/kg/day. Most differences in the 2.0 mg/kg/day arm were slight, though the clinically meaningful benefit in TTSTAND velocity at 24 weeks had disappeared by 48 weeks. Given the known variability around treatment outcomes with glucocorticoids, the small sample size, and uncertainties in the rate of disease progression in DMD, the EAG was unable to determine if the trend for outcomes to reduce after 24 weeks in the 2.0 mg/kg/day arm were due only to chance or whether there was evidence of treatment waning. However, the EAG did consider the evidence to suggest that there was no evidence of a continued improvement in outcomes after 24 weeks of treatment.

Table 19: Change from baseline at Week 24 and Week 48

	Vamorolone 2.0 mg/kg/day (n=30)	**Vamorolone 6.0 mg/kg/day (n=28 at week 24 and n=26 at week 48)**
TTSTAND velocity (rises/sec)		
LSM (SE) change from baseline at week 24	[redacted]	[redacted]
LSM (SE) change from baseline at week 48	[redacted]	[redacted]
6MWT distance (metres)		
LSM (SE) change from baseline at week 24	[redacted]	[redacted]
LSM (SE) change from baseline at week 48	[redacted]	[redacted]
TTRW velocity (metres/sec)		

	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28 at week 24 and n=26 at week 48)
LSM (SE) change from baseline at week 24	[redacted]	[redacted]
LSM (SE) change from baseline at week 48	[redacted]	[redacted]
NSAA score (0-34)		
LSM (SE) change from baseline at week 24	[redacted]	[redacted]
LSM (SE) change from baseline at week 48	[redacted]	[redacted]

Abbreviations: 6MWT, Six-minute walk test; kg, kilogram; LSM, least squares mean; mg, milligram; n, number; NSAA, North Star Ambulatory Assessment; SE, Standard error; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine.

Switch from prednisone to vamorolone

In Section B.2.6.2.5. of the CS, the company presented a comparison of the 28 participants who were randomised to vamorolone 6.0 mg/kg/day for 48 weeks to 15 participants who were randomised to prednisone for 24 weeks followed by vamorolone 6.0 mg/kg/day for 24 weeks. These data were presented as line graphs only, without the accompanying data points, and therefore the findings lacked precision for appraisal. These charts were presented in Doc B of the CS, figures 12 – 15.

The company claimed that the charts demonstrated that [redacted] after participants were switched to vamorolone 6.0 mg/kg/day. In general, outcomes for both arms (vamorolone-vamorolone and prednisone-vamorolone) [redacted] was noticeable for those switching from prednisone to vamorolone, though error bars around the effects were wide and overlapping (presumably leading to the company's conclusion of no reduction in effect). The EAG disagreed with the company somewhat – while it concluded that there was no clear evidence that treatment outcomes reduced after switching from prednisone to vamorolone, the evidence nevertheless suggested that this was possible. Given evidence that prednisone may outperform vamorolone for clinical outcomes, the EAG considered it plausible that longer follow-up data would show a reduction in treatment effect following a switch from prednisone to vamorolone 6.0 mg/kg/day.

As the company did not report data points for these outcomes, the EAG was also unable to appraise whether the effect of vamorolone following receipt of prednisone was consistent with the treatment effect when participants were steroid naïve. The effect of sequencing on treatment effects is a remaining uncertainty in this appraisal (Key Issue 2).

3.2.3.3. VBP15-LTE clinical effectiveness results

The company reported efficacy data from the VBP15-LTE trial in Table 31 in Section B.2.6.3 of the CS. The company stated that participants initiated on the higher doses of vamorolone (those evaluated in VISION-DMD; 2.0 and 6.0 mg/kg/day) had better clinical outcomes after 6 months' of treatment compared with those initially treated with lower doses (0.25 or 0.75 mg/kg/day). No data were presented for the lower dose treatment arms, and all data in the CS from VBP15-LTE were for the higher dose arms. Mah et al. (2022)[14] provided a more complete view of the VBP15-LTE results and the EAG present these in an adapted table below (Table 20) showing the difference between outcomes after 6 and 30 months' of treatment.

Broadly speaking, results after 6 months of treatment at the start of VBP-LTE were comparable with those reported in VISION-DMD. The results showed a reduction in TTSTAND velocity between 6 and 24 months, though overall outcomes appeared to be stable.

Table 20: Summary of efficacy outcomes from VBP15-LTE in participants who maintained a vamorolone dose at 2.0 mg/kg/day or more

Parameter	Mean (SD) after 6 months' treatment	Mean (SD) after 30 months' treatment
TTSTAND velocity in rises/sec (n=23)	0.25 (0.10)	0.20 (0.13)
TTCLIMB velocity in tasks/sec (n=23)	0.31 (0.13)	0.32 (0.19)
TTRW velocity in metres/sec (n=23)	1.90 (0.34)	1.87 (0.63)
6MWT in metres walked (n=20)	377.9 (64.77)	369.9 (77.81)
NSAA score (n=23)	22.3 (4.72)	21.78 (7.86)
Height percentile (n=23)	32.26 (26.87)	37.03 (31.14)
BMI z score	1.28 (0.51)	1.52 (0.66)
PODCI upper extremity and physical function (n=18)	75.34 (15.09)	82.32 (10.91)
PODCI transfer and basic mobility (n=19)	86.55 (9.21)	81.44 (17.54)

Abbreviations: 6MWT, Six-minute walk test; BMI, Body Mass Index; n, number; NSAA, North Star Ambulatory Assessment; PODCI, Paediatric Outcomes Data Collection Instrument; SD, Standard deviation; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine

Source: Mah et al. (2022)[14]

3.2.3.4. Adverse effects

In this section we present an overview of the evidence for treatment-emergent adverse events (TEAEs) and selected adverse events that are common adverse effects of glucocorticoid treatments in people with DMD.

Treatment-emergent adverse events

The company reported TEAEs in participants in the treatment and comparator arms at 24 weeks in Table 33 and Table 34 in Section B.2.10.1.2 of the CS. The number of participants experiencing TEAEs were similar across all four treatment arms (range 79.3% to 89.3%). A [redacted] in the vamorolone dose arms and prednisone arm had TEAEs leading to dose interruption. There was [redacted] reported in the prednisone arm and [redacted] in the vamorolone 2.0 mg/kg/day arm. One TEAE led to [redacted] and one led [redacted], both in the [redacted], but [redacted] in any of the treatment arms.

Overall, there were no meaningful differences in TEAE between prednisone and vamorolone after 24 weeks of treatment. TEAEs were only slightly increased for vamorolone and prednisone as compared to placebo, though there may be a small increased risk of serious and severe TEAEs

Table 21: Summary of TEAEs at 24 weeks

	Placebo (n=29)	**Prednisone (n=31)**	**Vamorolone 2.0 mg/kg/day (n=30)**	**Vamorolone 6.0 mg/kg/day (n=28)**
TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
TEAEs leading to dose interruption (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to withdrawal from treatment (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to withdrawal from study (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to death (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: kg, kilogram; mg, milligram; n, number; TEAE, treatment emergent adverse events.

Source: CS, reproduced from Table 33, Document B

AEs at week 48 of VISION-DMD were briefly summarised in Section B.2.10.2 of the CS. The company noted that no deaths occurred during the trial but three serious adverse events, all in the vamorolone 6.0 mg/kg/day arm, occurred between week 24 and week 48 of the trial. These events were perforated appendicitis, asthma, and viral gastroenteritis, and were all considered unrelated to treatment with vamorolone.

A summary of AEs experienced by participants during VBP15-LTE was presented in Section B.2.10.3. of the CS and has been reproduced in **Error! Reference source not found.**, below. These data were based on participants receiving varying doses between 2.0 and 6.0 mg/kg/day. The company stated that there were two serious TEAEs: moderate pneumonia in one participant and severe myoglobinuria, which occurred twice in one participant. One participant withdrew from the study due to moderate muscle weakness. The company noted that 10 participants (24.4%) treated with vamorolone at 6.0 mg/kg/day deescalated to 2.0 mg/kg/day owing to a TEAE of weight gain, and that weight gain abated among six participants after dose reduction.

Table 22: Summary of TEAEs, VBP15-LTE

	0.25 mg/kg/day (n=11)	0.75 mg/kg/day (n=23)	2.0 mg/kg/day (n=38)	4.0 mg/kg/day (n=3)	6.0 mg/kg/day (n=41)
Any TEAE, n (%)	4 (36.4)	14 (60.9)	29 (76.3)	1 (33.3)	39 (95.1)

	0.25 mg/kg/day (n=11)	**0.75 mg/kg/day (n=23)**	**2.0 mg/kg/day (n=38)**	**4.0 mg/kg/day (n=3)**	**6.0 mg/kg/day (n=41)**
Any Treatment-related TEAE	0	0	8 (21.1)	1 (33.3)	23 (56.1)
Any TEAE with CTCAE Grade ≥ 3	0	1 (4.3)	0	0	1 (2.4)
Any TEAE Leading to Discontinuation of Study	0	0	1 (2.6)	0	0
Any SAE	0	1 (4.3)	0	0	1 (2.4)
Any Serious TEAE	0	1 (4.3)	0	0	1 (2.4)

Abbreviations: AE, adverse events; CTCAE, Common Terminology Criteria for AEs; n, number; TEAE, treatment-emergent adverse events

Source: Company Submission, Document B, Table 38

Behavioural outcomes

After 24 weeks, there was an increased risk of behavioural problems with prednisone compared to all other treatment options. The severity of these behaviour problems was unclear, but the company noted that [redacted] in the [redacted] [redacted] the study because of [redacted] and one participant displayed aggression characterised as severe (CTCAE grade 2) who remained in the trial. At 48 weeks, there was a reduction in the number of people experiencing behavioural problems following treatment with vamorolone. Behavioural outcomes were not reported for VBP15-LTE.

Weight gain

Weight gain can be an adverse effect of treatment with glucocorticoids. After 24 weeks of treatment, there was an increased risk of weight gain following vamorolone 6.0 mg/kg/day as compared to prednisone or placebo, though event rates were small. In the trial CSR, the company reported that [redacted].

Table 23: Adverse events of special interest

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
At least 1 clinically relevant AE	[redacted]	[redacted]	[redacted]	[redacted]
Behaviour problems	[redacted]	[redacted]	[redacted]	[redacted]
Cataracts and glaucoma	[redacted]	[redacted]	[redacted]	[redacted]
Cushingoid features	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Infections	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal disorder	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic conditions	[redacted]	[redacted]	[redacted]	[redacted]
Skin/hair changes	[redacted]	[redacted]	[redacted]	[redacted]
Weight gain	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse events; kg, kilogram; mg, milligram; n, number; TEAE, treatment emergent adverse events.

Source: CS, reproduced from Table 36, Document B

Stunted growth

Stunted growth may occur naturally in those with DMD and may be exacerbated with the use of steroid treatment. At clarification (Question A9), the company reported the change from baseline in height Z-score at 24 weeks. Z-scores for height were calculated in comparison with age- and sex-standardised growth charts for the USA,[10,20] and the z-scores therefore represent the comparability of participants' height with those in a non-DMD population. Positive z-scores represent a better outcome than the cohort, while negative z-scores represent a poorer outcome.

[redacted]

(Table 24).

Table 24: Height Z-score change from baseline to Week 24

Height Z-score change	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)	Prednisone (n=31)	Placebo (n=29)
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (SE) vs prednisone	[redacted]	[redacted]	NA	NA
95% CI vs prednisone	[redacted]	[redacted]	NA	NA
p-value vs prednisone	[redacted]	[redacted]	NA	NA
LSM difference (SE) vs placebo	[redacted]	[redacted]	NA	NA
95% CI vs placebo	[redacted]	[redacted]	NA	NA
p-value vs placebo	[redacted]	[redacted]	NA	NA

Abbreviations: CI, Confidence interval; kg, kilogram; LSM – least squares mean; mg, milligram; n, number; SD, standard deviation; SE, standard error.

Source: reproduced from Table 9 in the clarification response

However, the company presented figures to suggest that after 48 weeks' of treatment, participants receiving [redacted] (see **Error! Reference source not found.**). The EAG noted that changes in height z-score at 48 weeks were small, though agreed with the company that [redacted] in participants receiving vamorolone in the trial. Clinical expert advice to the EAG was that even small benefits in height at this length of follow-up may be meaningful if they represent a trend away from growth stunting. However, the EAG considered that further follow-up data would be needed to determine if these data represent a trend for this outcome.

Figure 5: Height Z-score changes from period 1 prednisone switch to vamorolone

Source: CS, Figure 20, Document B

Bone health and fractures

In Section B.2.10.2.2, the company reported the results of bone health outcomes at 24 weeks as assessed using lumbar spine bone mineral content (BMC) and bone mineral density (BMD). The bone health through lumbar spine and total body BMC and BMD was reported in the VISION-DMD clinical study report (CSR)[21] and adapted for this report in Table 25.

The results showed a [redacted] in percent change from baseline in lumbar spine BMD and lumbar spine BMC. However, the EAG considered that this should be interpreted with caution due to missing data at baseline and at 24 weeks. The EAG was unclear how to interpret changes in lumbar spine BMD and BMC outcomes and was unable to obtain clinical expert views on this issue within the timeframe of the appraisal. However, the EAG noted that lower lumbar spine BMD and BMC was a risk factor for vertebral fracture.

Table 25: Percent Change from Baseline to Week 24 in Lumbar Spine BMD and BMC

	Placebo (n=29)	**Prednisone 0.75 mg/kg (n=31)**	**Vamorolone 2.0 mg/kg (n=30)**	**Vamorolone 6.0 mg/kg (n=28)**
Lumbar spine BMD (L1-L4), g/cm^2				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo (n=29)	Prednisone 0.75 mg/kg (n=31)	Vamorolone 2.0 mg/kg (n=30)	Vamorolone 6.0 mg/kg (n=28)
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Percent Change from Baseline at 24 weeks				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Lumbar spine BMC (L1-L4), g				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Percent Change from Baseline at 24 weeks				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMC, Bone mineral content; BMD, Bone mineral density; n, number; SD, standard deviation

In Section B.2.10.1.2 of the CS, the company reported on treatment-emergent vertebral fractures during 24-week trial treatment period one in VISION-DMD. No vertebral fractures occurred in either vamorolone arm, one fracture occurred in the placebo arm, and one fracture in the prednisone arm. Given the small number of events in this data set, the EAG considered that this result could have occurred by chance and so further evidence is needed to determine any effect for this outcome. The EAG's clinical experts warned that benefits and harms in bone and growth-related outcomes may occur over a longer time period than 24 weeks.

The company used the fracture data from VBP15-LTE as an input in the economic model. At 30-months follow-up, six participants (13.0%) were observed to have a total of seven clinical fracture events according to local site adverse event reporting, including one participant with a vertebral fracture and a foot fracture on two separate occasions, three participants with an upper limb fracture, one participant with a vertebral compression fracture, and one participant with multiple vertebral fractures. The EAGs clinical experts noted that vertebral fractures are a known adverse event linked to steroid treatment and these do not occur in those who are untreated. However, limb fractures occur in both untreated and treated people with DMD. The company did not detail the treatments arms of the people who sustained fractures and it was unclear if the fractures are linked to the dose of vamorolone participants were using.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In Section B.2.9 of the CS, the company stated that no formal indirect treatment comparison was conducted as the VISION-DMD study captured all clinical evidence of interest. However, a post-hoc, cross-study, indirect comparison, was conducted to compare vamorolone with prednisone and deflazacort. This comparison used data from VISION-DMD[10,11], VBP15-LTE and the FOR-DMD[14] trial, which compared different regiments of prednisone and deflazacort. The aim of the company's analysis was to compare treatment arms over a longer duration than the 24-week head-to-head comparison available from VISION-DMD.

The FOR-DMD trial[4] was a double-blind, Phase III, RCT to evaluate different glucocorticoid regimens in 196 ambulatory boys aged 4 to <7 years with DMD who were glucocorticoid-naïve at study entry. The study randomised participants to daily dosing of deflazacort, daily dosing of prednisone, or intermittent dosing of prednisone. The company also noted that the FOR-DMD Co-Study Chair, Dr Michela Guglieri, was also Study Chair for VISION-DMD and the two trials used similar methods, including comparable outcome measures, overlapping recruitment sites, similar treatment regimens (same prednisone and placebo tablets used for both studies; same treatment bands for prednisone dose), an overlap of treatment duration (48-week assessment); and similar study populations. The EAG considered that given the similarity in methods, including populations recruited, outcome measures collected, and recruitment sites, the studies were sufficiently similar to compare to one another.

The indirect comparison compared prednisone 0.75 mg/kg/day (n=55) or deflazacort 0.9 mg/kg/day (n=49) from FOR-DMD to:

- vamorolone 2.0 mg/kg/day (n=28) or vamorolone 6.0 mg/kg/day (n=28) in the VISION-DMD study (up to 48 weeks), or
- vamorolone dosing between 2.0–6.0 mg/kg/day (n=46) in the VBP15-LTE study (up to 2.5 years)

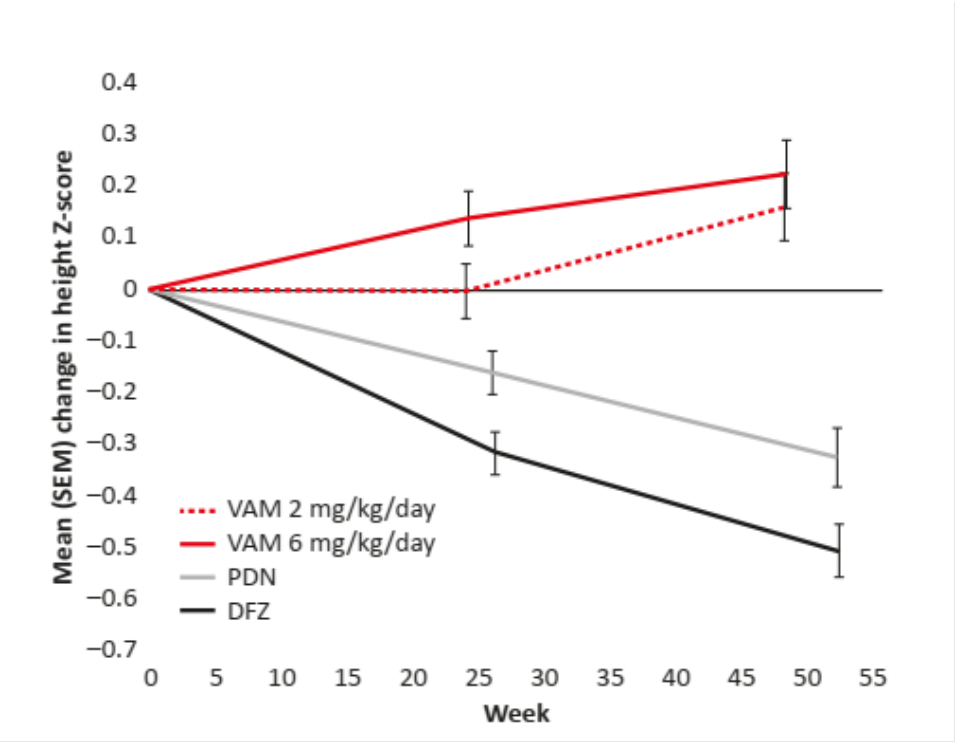
3.4. Critique of the indirect comparison and/or multiple treatment comparison

Despite the comparability of outcome measures between the trials in the indirect treatment comparison, the CS did not contain the results of clinical outcome measures across the treatment arms. The EAG was also unable to identify a publication of such an analysis. The

EAG considered that such a comparison would have augmented the evidence base for vamorolone by providing more evidence of its effectiveness in comparison to the alternative glucocorticoid treatments.

In the CS, the company reported difference in height Z-score after 1 year. The results showed that participants in the vamorolone arms had increased height Z-scores and participants in the prednisone and deflazacort arms had decreased height Z-scores from baseline. All changes were within one standard deviation of population norms.

Figure 6: Mean (SEM) change from baseline in height z-scores



Abbreviations: DFZ, deflazacort; PDN, prednisone; SEM, standard error of the mean; VAM, vamorolone

3.5. Conclusions of the clinical effectiveness section

The results of the company's clinical trials showed that participants receiving both vamorolone and prednisone showed meaningful improvements in muscle function compared to placebo after 24 weeks of treatment. However, vamorolone did not out-perform prednisone, and there were trends for vamorolone to have meaningfully poorer outcomes than prednisone after 24 weeks (Key Issue 1). Following this timepoint, participants receiving vamorolone did not show further

improvements, and treatment effects appeared to remain stable, potentially up to 30 months later. As there was no comparison arm in the trials beyond 24 weeks, it was not possible to determine whether clinical outcomes following treatment with prednisone would also stabilise or change.

On the balance of probabilities, the EAG considered it likely that vamorolone would not be as effective as prednisone in slowing down disease progression in muscle function. This conclusion was reached despite the lack of statistical significance in differences between vamorolone and prednisone at 24 weeks, which the EAG considered may be due to the small sample sizes in the trial and the anticipated variability in treatment outcomes for participants in all treatment arms. Further comparative evidence between vamorolone and prednisone (or deflazacort) at later timepoints would be useful for determining to what extent muscle function outcomes would be different with vamorolone. The EAG noted that the company could have reported the results of an indirect comparison between vamorolone trials and prednisone and deflazacort data from FOR-DMD. These data may have been informative for the appraisal, despite the limitations of naïve comparisons in general.

The EAG also noted that outcomes specified in the NICE scope that were not captured in the evidence base for vamorolone included short-term PROMs and medium- to long-term clinical outcomes that would demonstrate the implications of altered treatment effects on disease progression, such as the number of falls experienced by participants, and time to event outcomes for when people with DMD develop scoliosis or require use of a wheelchair. On the basis of the current evidence, it was therefore unclear to what extent any reduction in treatment effect with vamorolone would impact on the lives of people with DMD, including any long-term consequences.

As suggested by the company, the main potential benefit of vamorolone may be the reduced incidence of specific adverse effects that impact on the lives of people with DMD receiving existing treatment options, such as weight gain, stunted growth, behavioural issues and bone health. While data for these outcomes were based on short follow-up and were uncertain due to low event rates, the data were promising and suggested that the risks of these outcomes may be lower with vamorolone.

On the basis of the above conclusions, the EAG considered that vamorolone may be a preferred treatment option for some parents on the basis of its safety profile, despite the risk that it may not be as effective at maintaining muscle function as existing treatments. As is

current practice, parents may choose between vamorolone and existing treatments in order depending on their preferences and according to treatment response. This may mean that, contrary to the evidence available in the CS, vamorolone may be administered at a subsequent treatment line and not in a population who are naïve to glucocorticoids. The EAG considered it plausible that treatment effects for vamorolone may vary according to the line of treatment, though there was an absence of evidence to determine this (Key Issue 2). This was therefore a remaining uncertainty in the clinical effectiveness evidence for this appraisal.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted a SLR of previous economic evaluations, the searches for which were considered adequately structured and executed using a good range of sources. However, as noted in section 3.1, the EAG had some concerns over the quality of the search and its reporting. For example, only thesaurus terms were used to describe the interventions, and therefore the search may have missed articles not yet indexed, or poorly indexed. Zero search results are reported for Econlit, but when searched by PenTAG via EBSCOhost there were two relevant articles (although these were picked up via other databases in the company search). In addition, no details were provided of how supplemental searches were executed, and some numbers don't tally between the text and the Figure 1 PRISMA diagram.

The EAG was also unclear as to the extent to which the findings from the SLR informed the company's approach to patient utility assumptions and other model parameters. For example, from the economic evaluation SLRs, it seems that only one of the HRQoL studies retrieved from the search, Landfeldt 2017[22], was used in the building of the model. Rather, the company made extensive use of Noble-Longster et al 2022,[23] and Evans 2020[24], unpublished burden of illness (BOI) studies from the project HERCULES, which were not retrieved from the search. Many of the health state costs and resource data were also taken from these BOI studies, or other studies not retrieved from the search. There was therefore a lack of clarity in how the company selected the studies used to inform parameters in the model. However, given the model was based on the HERCULES natural history model, there is a logic to the use of the those data. Nevertheless, a full critique of other studies would have strengthened the company's choice of inputs. The EAG was therefore uncertain about the reliability of some of these resource and utility estimates used.

Table 26. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The company conducted a SLR of previous economic evaluations, the searches for which were executed using a suitable range of sources, although as noted in section 3.1, the EAG had

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		some concerns over the quality of the search and its reporting.
Inclusion criteria	Appendix G, Table 8	The inclusion PICO criteria were suitable for the decision problem. The company included cost-effectiveness, cost-utility analysis, cost-benefit and cost-minimisation analyses, and EEACTs (Economic Evaluation alongside Clinical Trials). Burden of disease, resource use and budget impact studies were excluded.
Screening	Appendix, D1.1	The EAG considered the methods for screening to be adequate. Only cost-effectiveness studies from a UK perspective were included.
Data extraction	Appendix, D1.1	The EAG was satisfied with the data extraction process.
QA of included studies	Appendix G, Table 12	Quality assessment was provided by using the Drummond and Jefferson criteria

Abbreviations: CS, Company Submission; EAG, External Assessment Group; EEACTs, Economic Evaluation alongside Clinical Trials; HRQoL, health-related quality of life; PICO, Population Intervention Comparator Outcome; QA, quality assessment; SLR, systematic literature review; UK, United Kingdom

Table 27. Summary of EAG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The company conducted a SLR of HRQoL articles relevant to the decision problem, the searches for which were executed using a suitable range of sources, although as noted in section 3.1, the EAG had some concerns over the quality of the search and its reporting.
Inclusion criteria	Appendix G, Table 9	The inclusion PICO criteria were suitable for the decision problem. The company included RCTs, non-RCTs, observational studies, HRQoL elicitation and validation studies, economic evaluations, cost-utility analyses, and EEACT (Economic Evaluation alongside Clinical Trials). Individual cost study reports were excluded.
Screening	Appendix, D1.1	The EAG considered the methods for screening to be adequate.
Data extraction	Appendix, D1.1	The EAG was satisfied with the data extraction process.
QA of included studies	N/A	No quality assessment was performed.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

Table 28. Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The company conducted a SLR of healthcare resource use and costs articles relevant to the decision problem, the searches for which were executed using a suitable range of sources, although as noted in section 3.1, the EAG had some concerns over the quality of the search and its reporting.
Inclusion criteria	Appendix G, Table 10	The inclusion PICO criteria were suitable for the decision problem. The company included the economic evaluation study types described above, plus cost, burden of disease and resource use studies. Individual case studies were excluded.
Screening	Appendix, D1.1	The EAG considered the methods for screening to be adequate.
Data extraction	Appendix, D1.1	The EAG was satisfied with the data extraction process.
QA of included studies	N/A	No quality assessment was performed.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 29: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate, which captured the health benefit to patients. The company included carer disutility within their base case.
Perspective on costs	NHS and PSS	The company included a number of non-reference case costs in its estimate of health state costs in its base case (eg

Attribute	Reference case	EAG comment on company's submission
		non-medical costs and transfer payments).
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis, presenting pairwise results versus a pooled comparator. The model submitted by the company was a Markov model. The EAG considered that the company's decision model was broadly appropriate for decision making but that a pooled comparator risks biasing estimates of incremental cost-effectiveness.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company used a 50 year time horizon in the base case analysis. The EAG considered that this was long enough to capture key differences in costs and QALYs between vamorolone and SoC over time.
Synthesis of evidence on health effects	Based on systematic review	Clinical data used in the economic model were derived from multiple sources inlcuding VISION DMD, FOR DMD and the long-term extension study (LTE). Additionally, the company used published literature and assumption when data were unavailable.
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.	EQ-5D scale was noted to lack sensitivity for DMD in the CS and hence condition specific preference based measure DMD-QoL has been used to derive patient utilities (as per BOI study[23]) and EQ-5D for carer utilities (based on Landfeldt et al 2017[22]).
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The company has used the QALY shortfall approach. A 1.7x severity modifier has been applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	Some resource use and costs were primarily based on NHS reference costs 2021/2022 and the PSSRU (2022), as

Attribute	Reference case	EAG comment on company's submission
	valued using the prices relevant to the NHS and PSS	appropriate. The EAG noted that health state costs were based on direct and indirect medical costs from a burden of illness study which included a number of out of scope items (eg out of pocket costs and transfer payments)[24]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and QALYs were discounted at 3.5% as appropriate.

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal; DMD-QoL, Duchenne Muscular Dystrophy Quality of Life Measure

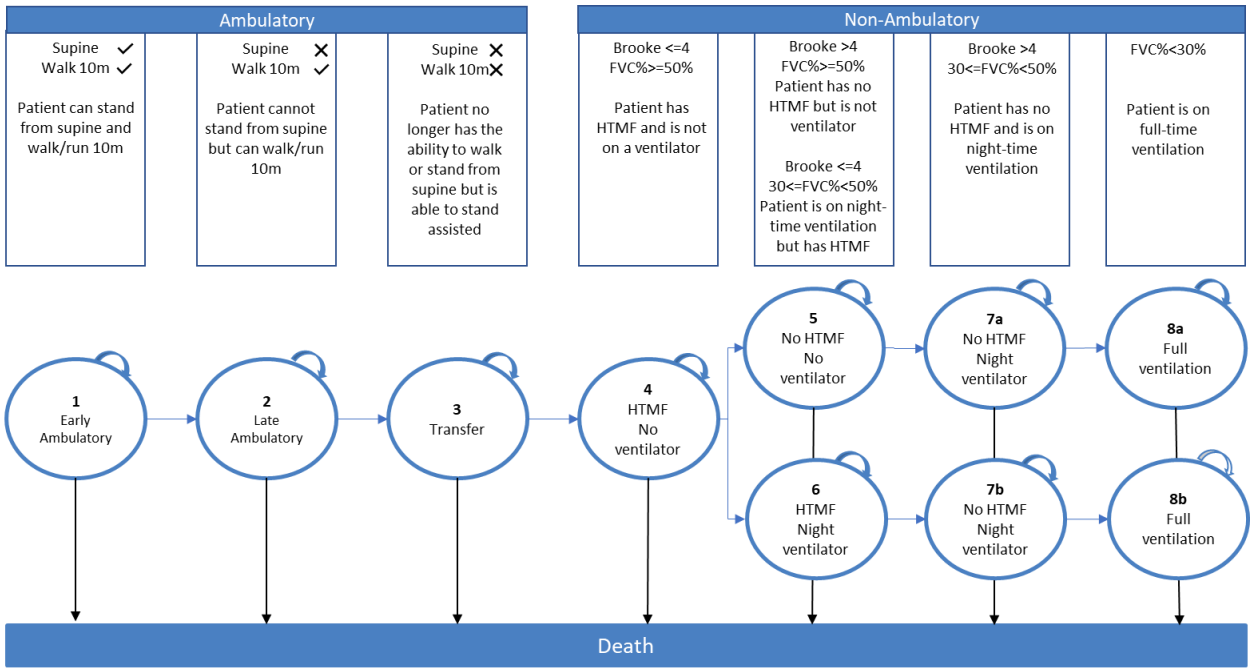
4.2.2. Model structure

The company's model was based on the HERCULES natural history model of disease progression of patients with DMD.[25] It comprised a Markov model consisting of eight health states, and death as the absorbing state. The health states were clearly defined and structured around a patient's ambulatory status, Brooke score[26] (with a cut-point at ability to self feed), FVC% and requirement for nocturnal or full time ventilation (Figure 7).

Patients progress through the model according to transition probabilities. Progression was only permitted towards more severe health states (i.e. disease reversal was not possible). This was consistent with clinical opinion to the EAG that characterised DMD as progressive in nature with no improvement in health status observed with time. Furthermore, the HERCULES model appeared to be appropriate to reflect the UK population with DMD.

The EAG considered the structure of the model to be appropriate to address the decision problem.

Figure 7: Model Schematic



Source: CS, Figure 21.

4.2.3. Population

The average starting age in the model was 4.1 years, based on a UK study by Vry et al.[27] It was not clear why the company opted to use Vry et al. to derive baseline age, as opposed to the pivotal trial (VISION DMD). It may have been due to the multicentred nature of VISION DMD and therefore relatively limited generalisability to UK patients, although 6/33 centres in the study were UK based. It was also consistent with the licensed starting age of 4 years. The company provided a sensitivity analysis which increased the starting age to 5.1 years, in line with the average age within VISION-DMD (5.41 years). Results were somewhat sensitive to this analysis.

Clinical opinion to the EAG confirmed that children with DMD are likely to start steroids at approximately 4 years of age, with most starting between the ages of 4 and 6 years. Overall, the EAG considered the company's base case age to be appropriate. However, for completeness a scenario analysis was conducted with a starting age of 5 years.

4.2.4. Interventions and comparators

The primary comparator included in the economic analysis was standard of care (SoC), which was assumed to consist of prednisone or deflazacort, expressed as a blended comparator assuming 85% of patients take prednisone and 15% take deflazacort (this affects costing estimates described in Section 4.2.8 below and some adverse events). Clinical opinion to the EAG was that both prednisone and deflazacort were considered standard of care in the UK, however the proportion of new patients receiving each treatment was approximately 50/50. It was also noted that prednisone was used more by older children. Deflazacort was not offered in soluble form, which may influence uptake.

The EAG has concerns with pooling of comparators as they introduce scope for gaming and evading relevant comparisons of interventions along the efficient frontier. The EAG's preferred approach is to treat discrete treatment strategies as such and compare all in a fully incremental analysis, as per the NICE reference case.

The model allowed for down titration of dosing based on tolerability (Table 30). Clinical expert opinion to the EAG was that dosing would be reduced only if there were intolerable side effects. There would be a period where dose is increased in line with weight, provided that patients have good ambulation. However, once patients become non-ambulatory the dose is not increased and is more likely down-titrated. Clinical opinion to EAG also indicated that while patients might experience reduced efficacy with down-titration, it would still be better than having no treatment. Parents may be reluctant to increase dose, particularly if the treatment is considered to increase behavioural problems. The impact of dosing on cost and outcomes is considered in sections 4.2.6 and 4.2.8.

Table 30: Dosing regimens in the economic model

Drug	Starting dosing regimen	Dose reduction regimen	Source
Intervention			
Vamorolone	Aged 4 years and older: 6.0 mg/kg/day administered orally	May be down-titrated to either the below based on individual tolerability: • 4.0 mg/kg/day administered orally • 2.0 mg/kg/day administered orally	SmPC[11]; VISION-DMD[4]
SoC			

Drug	Starting dosing regimen	Dose reduction regimen	Source
Prednisone	0.75 mg/kg/day administered orally	0.53 mg/kg/day administered orally	25-33% dose reduction based on Birnkrant et al.[28]
Deflazacort	0.9 mg/kg/day administered orally	0.64 mg/kg/day administered orally	

Abbreviations: SmPC, summary of product characteristics; SoC, standard of care

4.2.5. Perspective, time horizon and discounting

Costs were estimated from an NHS and PSS perspective (albeit with some out of scope costs, see section 4.2.8 below). Additional scenarios were conducted including a broader (societal) cost scope. Outcomes were considered from the perspective of the patient and one carer. Costs and benefits were discounted at 3.5% as per the NICE reference case.

The time horizon used in the company's base case was 50 years. The company noted that 50 years was likely to be appropriate as *'DMD is a life-long condition that reduces life expectancy significantly, with a median life expectancy of 29.9 years (range 21.0-36.2) with ventilatory support'* (Landfeldt et al. 2020[29], cited in company submission, Table 42, P108). Based on clinical input to the EAG, the median life expectancy for people with DMD born before 1990 was approximately 28.1 years. However, post-1990, median life expectancy was likely to be higher. Clinical opinion to the EAG further confirmed that people with DMD were not likely to live beyond the age of 50 years. Overall, the EAG considered that 50 years was long enough to capture key differences in costs and benefits between vamorolone and SoC.

The cycle length used in the model was one month (with half cycle correction). Based on clinical input to the EAG, patients in the UK were likely to be reviewed or assessed every six months by a clinician, thus a six month cycle length may also be appropriate. However, the shorter cycle length allowed for greater resolution and granularity in the results. The EAG considers the one month cycle length to be appropriate to the decision problem.

4.2.6. Treatment effectiveness and extrapolation

The company considered the follow-up of the pivotal RCT (VISION-DMD[10,11]) too short to provide reliable estimates of transition probabilities for the model. It therefore did not use these data, preferring to use transition probabilities reflecting the natural history of disease already employed in the HERCULES model.[25] This was supplemented with two additional studies, FOR-DMD[4] and LTE[14], for extrapolation of the effectiveness of SoC and vamorolone, respectively.

Transition probabilities were based on steroid dosage (whether for SoC or vamorolone): either on treatment (full dose), off treatment, or down-titrated dose.

On-treatment transition probabilities, SoC and vamorolone: Natural History Model

The company used the natural history transition probabilities to represent the disease progression for patients taking the full dose of vamorolone and prednisone (6.0mg/kg/day and 0.75mg/kg/day, respectively). This is justified on the basis of *"vamorolone… show[ing] comparable efficacy to prednisone… in VISION-DMD"* (Company submission, Section B3.3.2, P109). However, the EAG's review of the results of VISION-DMD concluded there was some evidence for the superiority of prednisone over vamorolone (section 3.2.3). Whilst the EAG broadly agrees that the short follow-up time of VISION-DMD limits the scope for generation of transition probabilities, the EAG disagrees that the assumption of equal efficacy represents a conservative approach and explores a number of alternative scenarios in its own analyses (Sections 6.2 and 6.3).

Natural history transition probabilities in the HERCULES model are based on pooled individual patient data from 11 data sources including natural history studies, placebo arms of clinical trials, and disease registries. Eighty per cent of the patient cohort were taking steroids, but the type and dosing regimen were not stated. The company acknowledges this as a source of uncertainty. On balance, the EAG considers the natural history model a suitable source for transition probabilities.

Off-treatment transition probabilities, SoC and vamorolone

McDonald et al. (2018)[2] reported Kaplan-Meier estimates of time to ambulatory milestones for patients on GC for over one year and for those who were either untreated or received GC for less than a month. The company assumed that the two arms represented on and off treatment for SoC and vamorolone. Hazard ratios were calculated from fitting a Cox proportional hazards model to each pair of curves representing time to certain milestones. Transition probabilities were modified by the estimated hazard ratios.

Overall, the EAG considered this approach somewhat crude and at high risk of bias but was reasonable and likely the best option given the data available.

Titrated dose transition probabilities, SoC

Data from FOR-DMD (2022),[4] an RCT of differing steroid dosing regimens in DMD, were reviewed to estimate hazard ratios for ambulatory milestones. The company stated the resulting HRs lacked face validity as they implied worse outcomes than no steroids. Clinical advice to the company was to adopt a 60% relative effect (i.e. a 40% reduction in effect). The company opted for a larger 40% relative effect (i.e. a 60% reduction in effect) in its base case as a mid-point between clinical opinion and the FOR-DMD data, exploring 60% (and 20%) in a scenario analysis. The EAG considered this a reasonable solution. It was, however, noted that this was applied only to the SoC arm, and not suboptimal dosing of vamorolone. Clinical advice to the EAG was that this was unlikely. The EAG therefore explored alternative scenarios in its analyses, and adopted a symmetric approach in its base case (see section 6.2.2).

Mortality

The HERCULES model does not implement an age-related mortality, with mortality dependent only on health state. The company therefore modified the transition probabilities for patients aged 30 and over from states 8a and 8b to death (doubling the mortality risk from ~0.32% per week to ~0.65%), following a review of an individual patient data meta-analysis.[30] The cut-off of 30 years was selected as the median survival of patients with DMD. In addition, age-specific mortality was compared with general population mortality, with the chosen value being whichever was the higher of DMD or general population levels. The EAG considered the adjustment for general population mortality to be plausible, but as the post-30 years of age increase represented a modification to what is designed as a natural history model, the EAG explored the impact of excluding the mortality boost at 30 years in a scenario.

Adverse events

Adverse events were divided into adverse events of special interest (AESIs) and acute events. In addition, the model also included stunted growth, incidence of fracture (spinal and other), and scoliosis.

AESIs included weight gain, behavioural issues, and Cushingoid features *inter alia*, whilst acute events were diarrhoea, vomiting, pyrexia (fever), and cough (Table 31 and Table 32). Data for AESIs and acute events for vamorolone and prednisone patients were extracted from VISION-DMD.[10,11] The placebo arm of VISION-DMD was used to represent the incidence of events for patients who were off treatment. Incidence of stunted growth in the prednisone arm was based

on a six-year follow-up of a case-series of boys receiving daily steroids.[6] The company assumed zero stunted growth in the vamorolone arm. Incidence of AESIs for down-titrated doses of prednisone were adjusted for rate ratios from FOR-DMD.[4] Adverse events were assumed the same in the vamorolone arm, regardless of dose.

The EAG noted that the company only included moderate to severe events in its primary analysis, despite an AESI being defined as any which is 'severe and sudden in onset' (company submission p118), although the company conducted a scenario including all adverse events. The EAG noted that excluding the less severe events resulted in a substantially lower incidence included in the model compared with the trial data (see Table 31 and Table 32 below). Whilst inclusion of only moderate and severe adverse events is a common pragmatic approach in decision modelling, given (1) the side effect profile of vamorolone vs other steroids is pivotal to the company's value proposition and (2) all AESIs being considered severe by definition, the EAG conducted scenario analyses around this.

Table 31: Adverse event rates per monthly cycle used in model

Treatment	Vamorolone	SoC (optimal dose)	SoC (sub-therapeutic dose)	Placebo	Source
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	VISION-DMD; rate over 24 weeks Sub-therapeutic SoC AE rates calculated from ratio in FOR-DMD.
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	
Cough	[redacted]	[redacted]	[redacted]	[redacted]	
Weight gain	[redacted]	[redacted]	[redacted]	[redacted]	
Behavioural issues	[redacted]	[redacted]	[redacted]	[redacted]	
Cushingoid effects	[redacted]	[redacted]	[redacted]	[redacted]	
Immune suppressed/infection	[redacted]	[redacted]	[redacted]	[redacted]	
GI symptoms	[redacted]	[redacted]	[redacted]	[redacted]	
Diabetes	[redacted]	[redacted]	[redacted]	[redacted]	
Skin/Hair change	[redacted]	[redacted]	[redacted]	[redacted]	
Stunted growth	0.00%	1.75%	1.44%	0.00%	Wong et al.; rate over 6 years

Abbreviations: AESI, adverse event of special interest; GI, gastrointestinal.
Source: Company Submission Document B Table 51, p118.

Table 32: Adverse events of special interest as reported in VISION-DMD (incidence over 24 weeks)

	Vamorolone 6.0 mg/kg/day (n=28)	Prednisone (n=31)	Placebo (n=29)	Vamorolone 2.0 mg/kg/day (n=30)
At least 1 clinically relevant AE	[redacted]	[redacted]	[redacted]	[redacted]
Weight gain	[redacted]	[redacted]	[redacted]	[redacted]
Behaviour problems	[redacted]	[redacted]	[redacted]	[redacted]
Cushingoid features	[redacted]	[redacted]	[redacted]	[redacted]
Infections	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic conditions	[redacted]	[redacted]	[redacted]	[redacted]
Skin/hair changes	[redacted]	[redacted]	[redacted]	[redacted]
Cataracts and glaucoma	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal disorder	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event
Source: VISION-DMD CSR[6], reproduced from Company Submission, Table 36, p82 (column and row ordering changed to match Table 31)

Bone Health

Fractures were modelled as a function of health state, with higher rates of spinal vertebral fractures associated with SoC (prednisone and deflazacort) versus vamorolone, and lower rates of long bone fractures for SoC versus vamorolone or no treatment, albeit with some variation by health state (Tables 52 and 53 of company submission, pp119-20). Rates for SoC and off treatment were based on long-term follow-up data of cohorts of patients who did and did not take steroids (Perera et al. 2016[5]), and those for vamorolone were extracted from the LTE study and FOR-DMD. Overall, the EAG felt the approach possessed face validity and was reasonable given the data constraints.

The impact of scoliosis was included in the model via estimates of the proportion of individuals requiring spinal fusion surgery. Data from McDonald et al. (2018)[2] suggested that 29% of non-ambulatory patients have spinal fusion surgery over 10 years. However, the cohort comprised mostly (87%) participants who had received steroids. Clinical expertise suggested that surgery amongst those receiving steroids would be around 10%, whilst 90% of those off steroids would require it. The EAG considered this a reasonable assumption.

Discontinuation

In Section B.3.3.5 of the CS, the company stated that the discontinuation data used in the economic model for vamorolone and SoC were taken from VISION-DMD and the Cooperative International Neuromuscular Research Group (CINRG), respectively. The company reported discontinuations in prednisone, deflazacort, and prednisolone using the chart in Figure 8.

Figure 8: SoC discontinuation from Cooperative International Neuromuscular Research Group

Source: CINRG. Reproduced from CS, Figure 23, Document B

While the company stated that these data are taken from CINRG, no further details were provided in the CS as to the specific publication in which they were reported. The CINRG discontinuation data was reported for longer than 14 years as opposed to 24 or 48 weeks in VISION-DMD. The EAG did not consider discontinuation data after less than a year of treatment could reliably be extrapolated to a lifetime as discontinuation data gathered over 14 years of treatment. Also, the EAG noted that the proportion still on deflazacort plateaus at ~82% after six years while prednisone and prednisolone continued to decline to below 30% by 14 years. This lacked face validity and was further queried by clinical advisors to the EAG. The EAG were unable to critique these data as the company did not detail which specific publication(s) they were taken from.

In terms of parametric extrapolation, the original CS mentioned that due to small sample sizes the standard set of parametric functions produced implausible results. Therefore, exponential functions were fitted to the data in the original model submitted by the company. However, following clarification, the company included the standard parametric curves in the updated model and proposed that log-logistic be used in the base case. The EAG, however, noted that generalised gamma fits the KM data for prednisone and deflazacort more closely than log-logistic and therefore implemented it in the EAG base case.

Vamorolone was stopped in the base case after progression to health state 6 (requiring night-time ventilation), with alternatives explored in a scenario analysis. Patients who stop taking vamorolone or SoC experience the transition probabilities and risk of adverse events of the no treatment arm. Clinical advice to the EAG was that in the past it was common to stop steroid treatment on loss of ambulation, but patients may now continue after this point. However, treatment would not necessarily be ceased at health state 6. The EAG therefore explored an alternative stopping scenario (at loss of ambulation) based on the clinical advice received.

Down-titration

As well as discontinuation, the model allowed down-titration of dose (with associated transition probabilities described above). For SoC this was based on CINRG data, and for vamorolone, data from the named patient programme (NPP). The EAG noted that the impact of down titration was applied asymmetrically. That is, while patients on SoC who reduced their dose would experience reduced treatment effects (see the description of transition probabilities above), side effects, and lower drug acquisition costs, patients who reduced dose on vamorolone would maintain a full treatment effect (and side effects), but with lower drug acquisition costs. While clinical advice to the EAG confirmed that residual benefits are likely to be maintained post treatment cessation, the EAG did not consider the asymmetric approach to be plausible, and therefore explored alternative scenarios.

4.2.7. Health-related quality of life

EQ-5D data were collected within the VISION-DMD trial. However, the company cited evidence that EQ-5D is of limited sensitivity to changes in health status in people with DMD and therefore excluded these data from their analysis. The company's systematic review instead identified a number of studies reporting health state utilities, from which the company selected Landfeldt et al. (2017)[22] as the most appropriate. This used the HUI3 questionnaire to measure health status

of patients and was proxy completed by carers. Carers themselves completed the EQ-5D-3L to rate their own health status. An additional burden of illness (BOI) was identified (Noble-Longster et al. 2022[23]), conducted as part of the project HERCULES model, using the disease specific DMD-QoL.

The company's base case used patient utilities from the BOI study, and a blend of the Landfeldt and BOI studies for carer disutilities. to ensure consistency and face validity. Landfeldt et al. (2017) was used in scenario analyses.

Disutility due to adverse events was drawn from a number of sources, including previous technology appraisals. The EAG considered the magnitude of utility decrements to be broadly reasonable, but explored alternative value sets (section 6.2.10).

4.2.8. Resources and costs

4.2.8.1. Drug costs

Drug costs for vamorolone included a confidential patient access scheme (PAS) discount. List prices for deflazacort and prednisone were extracted from the BNF. The EAG noted that drug costs are linked to body weight, as the dosing is body weight dependent. However, there was no banding of dosing based on body weight mentioned in the CS. Also, the company assumed no change in body weight beyond 18 years of age. They instead applied a consistent body weight of 66.5 kg (the UK general population's 50th percentile weight). The EAG clarified the appropriateness of this assumption with a clinical expert, who mentioned that this assumption is not unreasonable given that for most boys with DMD weight gain happens before 18 years of age; they are less likely to gain weight beyond this. Although the possibility of weight gain beyond 18 years cannot be ruled out completely, the proportion of such patients is expected to be low. All treatments are oral and thus there were no administration costs, and zero wastage was assumed. Clinical advice to EAG confirmed that drug wastage is likely to be minimal. The EAG was confident that drug costs had been modelled appropriately.

4.2.8.2. Health state costs

Costs by health state were extracted from the BOI study, a part of project HERCULES. The study included direct medical care costs (excluding paid carer time, which may have been funded privately or provided by personal social services), as well as direct non-medical care costs. The EAG noted that direct medical costs included tests and procedures, medical devices, consultations, and hospitalisations. However, non-medical costs included home alterations, over

the counter medications, transport, transfer payments, alternative therapies, and 'other' costs. Home alterations may be funded by personal social services. However, over the counter medications, transport and alternative therapies represent patient out of pocket costs, and transfer payments are not funded by the NHS. Therefore, a substantial proportion of the health state costs are out of scope and are therefore inconsistent with the reference case. The EAG explored the impact of excluding the out of scope costs in scenario analysis.

4.2.8.3. Adverse event costs

The company assigned resource use associated with adverse events based on assumed contact with the health service. The EAG considered most of the unit costs assigned to be appropriate. The exceptions were the cost of growth hormone therapy for stunted growth (£6,451 per patient per year) and inclusion of indirect costs for spinal surgery for scoliosis. Clinical advice to the EAG suggested that growth hormones are rarely used in DMD in the UK, and indirect costs are out of scope of the reference case. Therefore the EAG explored a scenario excluding this cost.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

The company submission stated that a patient access scheme (PAS) discount for vamorolone is pending approval. This discount of [redacted] was incorporated into their model. Based on the deterministic results provided by the company, vamorolone, with the PAS discount, gave an ICER of [redacted] compared to SoC – based on an incremental QALY gain of [redacted] and an incremental cost of [redacted] (Table 33). Probabilistic results yielded higher incremental costs and lower incremental QALYs compared with the deterministic, resulting in an ICER of [redacted] (Table 34). The model from which these results are taken included a log-logistic parametric extrapolation of the proportion on treatment, which the company requested be considered the revised base case rather than that reported in the updated submission (see clarification response v2.0, Table 18 vs updated company submission, Table 78 P152). The company did not report probabilistic analyses in the clarification response but were available in the decision model.

Table 33: Company base case results (PAS price) – deterministic

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALY, Quality-adjusted life year; SoC, standard of care

Table 34: Company base case results (PAS price) – probabilistic

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£)
SoC	[redacted]	nr	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	nr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; nr, Not Reported; QALY, Quality-adjusted life year; SoC, standard of care

5.2. Company's sensitivity analyses

The results of the company's sensitivity analyses, including one-way sensitivity analyses (OWSA), scenario analyses and probabilistic sensitivity analyses (PSA), are outlined in the sections below.

5.2.1. One-way sensitivity analysis (OWSA)

The company provided a OWSA, which varied key model parameters from upper and lower CIs derived from literature or estimated from the pre-specified probabilistic distributions assigned to each parameter. The results are presented in Table 35.

The EAG noted three key matters pertaining to this analysis:

- The results were relatively insensitive to variation of the modelled parameters. The highest ICER was reported to be [redacted].
- No justification was provided for selecting the relatively short list of model input parameters.
- Although OWSA is useful in identifying the parameters that are likely to impact base case results, the EAG believed that the analysis was not useful to inform decision making. This was because parameters were varied individually and without context.

Table 35: Company OWSA results

Parameter name	Lower incremental costs	Upper incremental costs
Direct costs by health state (CPRD) - Comparator 1: 8 - Full time ventilation	[redacted]	[redacted]
Direct costs by health state (CPRD) - New treatment: 8 - Full time ventilation	[redacted]	[redacted]
Direct costs by health state (CPRD) - New treatment: 1 - Early ambulatory	[redacted]	[redacted]
Behavioural issues: Disutilities	[redacted]	[redacted]
Stunted Growth Costs	[redacted]	[redacted]
Behavioural issues: Caregiver Disutilities	[redacted]	[redacted]
Behavioural issues (caregiver): Duration of event (days)	[redacted]	[redacted]
Vamorolone - Average weight: Age 5	[redacted]	[redacted]
SoC Behavioural issues incidence per cycle: 8b - Full time ventilation	[redacted]	[redacted]

Abbreviations: BOI, burden of illness; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; OWSA, one-way sensitivity analysis; PAS, patient access scheme; QALY, Quality-adjusted life year; SoC, standard of care

5.2.2. Scenario analyses

The company provided scenario analysis results based on the original model using both list and PAS prices for vamorolone, as presented in Table 36 and Table 37. The EAG was initially unable to replicate some of the scenario results. Nonetheless, following clarification, the company provided the model settings used for those scenarios in their updated model.

Table 36. Company's scenario analyses results for vamorolone vs SoC – PAS price

#	Scenario	Deterministic ICER	Probabilistic ICER
	Base case	[redacted]	[redacted]
1	Time horizon – 40 years	[redacted]	[redacted]
2	Time horizon – 60 years	[redacted]	[redacted]
3	Annual discount rate for costs and QALYs – 1.5%	[redacted]	[redacted]
4	Vamorolone down-titration - All down titrate to [redacted]	[redacted]	[redacted]
5	Vamorolone down-titration - 50% down titrate to [redacted]	[redacted]	[redacted]
6	SoC down-titration efficacy - 60% of full efficacy	[redacted]	[redacted]
7	SoC down-titration efficacy - 20% of full efficacy	[redacted]	[redacted]
8	AESI all grades	[redacted]	[redacted]
9	Starting model cohort 5.41 years	[redacted]	[redacted]
10	Starting model cohort 5.41 years and 50% early ambulatory	[redacted]	[redacted]
11	Exclude carer QoL impact	[redacted]	[redacted]
12	Behavioural issues duration of AE – 1 year	[redacted]	[redacted]
13	Health state utilities (patient) – Landfeldt et al.	[redacted]	[redacted]
14	Health state costs (patient and societal) – Landfeldt et al	[redacted]	[redacted]
15	Vamorolone stopping rule at loss of HTMF	[redacted]	[redacted]
16	Vamorolone stopping rule at starting full-time ventilation	[redacted]	[redacted]

Table 37. Company's scenario analyses results for vamorolone vs SoC – list price

#	Scenario	Deterministic ICER	Probabilistic ICER
	Base case	[redacted]	[redacted]
1	Time horizon – 40 years	[redacted]	[redacted]
2	Time horizon – 60 years	[redacted]	[redacted]
3	Annual discount rate for costs and QALYs – 1.5%	[redacted]	[redacted]
4	Vamorolone down-titration - All down titrate to [redacted]	[redacted]	[redacted]
5	Vamorolone down-titration - 50% down titrate to [redacted]	[redacted]	[redacted]
6	SoC down-titration efficacy - 60% of full efficacy	[redacted]	[redacted]
7	SoC down-titration efficacy - 20% of full efficacy	[redacted]	[redacted]
8	AESI all grades	[redacted]	[redacted]
9	Starting model cohort 5.41 years	[redacted]	[redacted]
10	Starting model cohort 5.41 years and 50% early ambulatory	[redacted]	[redacted]
11	Exclude carer QoL impact	[redacted]	[redacted]
12	Behavioural issues duration of AE – 1 year	[redacted]	[redacted]
13	Health state utilities (patient) – Landfeldt et al.	[redacted]	[redacted]
14	Health state costs (patient and societal) – Landfeldt et al	[redacted]	[redacted]
15	Vamorolone stopping rule at loss of HTMF	[redacted]	[redacted]
16	Vamorolone stopping rule at starting full-time ventilation	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALY, Quality-adjusted life year; SoC, standard of care

5.2.3. Probabilistic sensitivity analysis

The company conducted a probabilistic analysis with 1,000 simulations but did not provide any analyses to demonstrate whether this was sufficient to minimise Monte Carlo error. Probabilistic results are reported above in Abbreviations: ICER, Incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALY, Quality-adjusted life year; SoC, standard of care

Table 34.

5.3. Model validation and face validity check

The company's model was based on the project HERCULES natural history model, with amendments reviewed by clinical experts for plausibility. The company also compared its estimates of QALYs accrued in the SoC arm with previously published studies.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations with the company's base case, and therefore explored the impact of using alternative assumptions and parameter values. The section is organised as follows:

- 6.1 details the impact of errors identified in the EAG's validation of the company's model.
- 6.2 presents a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and uncertainties identified by the EAG. These analyses were conducted within the company's (post-clarification) base case analysis.
- 6.3 presents the EAG's preferred base case, in both an incremental and cumulative manner.

6.1. EAG corrections and adjustments to the company's base case model

Besides several minor errors in terms of reporting, labelling and discrepancies between the CS (Document B) and the model, the EAG noted the following issues:

- The company's economic model applied a severity modifier to both patient and carer QALYs. The severity modifier is based on the QALY shortfall. However, as described in NICE guidance, "…QALY shortfall is defined as the amount of health lost by a person with a condition; other people, such as carers, should not be included".[31] The EAG therefore corrected this by applying the modifier only to patient QALYs.
- EAG noted a #VALUE! error in the probabilistic model parameters for generalised gamma (Cost Calcs sheet). This prevented the running of the PSA using a generalised gamma parametric extrapolation. The EAG did not have access to the data used to derive these parameters. However, it was identified that the variance (Q) in the covariance matrix was negative. This was subsequently fixed, which enabled the PSA to run. Nevertheless, the EAG is uncertain whether the fix applied fully resolved the issue, unless clarified further by the company.
- A formula was also found to be missing (in the 'HRQoL data' sheet of the model) for choosing patient utility values based on either the BOI study or Landfeldt et al. 2017. The sheet instead contained hard coded values based on BOI study rather than a formula

linking to HRQoL calculations. The EAG subsequently fixed this issue. No changes in the results were caused.

The EAG corrected company base case results – following the above changes – have been provided in Table 38 (disaggregated into the three discrete comparators with fully incremental analysis).

Table 38: EAG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company probabilistic base case					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted several scenario analyses to explore uncertainty surrounding certain model parameters and assumptions. The scenario analyses are listed below, with the associated results presented in Section **Error! Reference source not found.**.

6.2.1. Using an alternative starting age of the cohort

The EAG conducted an analysis in which the starting age of cohort was set to 5 years. This was based on clinical opinion to the EAG, which stated that starting the treatment was often delayed until 5 years of age, owing to delays in diagnosis. This scenario increased the ICER by 13%, as the total QALYs reduced slightly with the increased starting age. However, the results of this scenario should be interpreted with caution as the impact on treatment effectiveness or discontinuation could not be estimated (section **Error! Reference source not found.**).

6.2.2. Applying symmetric effect of down-titrated dose of SoC and vamorolone

In its base case the company assumed patients receiving standard of care would experience reduced treatment effectiveness, adverse events exposure and drug cost if the dose was down-titrated. Patients receiving vamorolone would experience maintained treatment effect, adverse events exposure but reduced cost. Clinical advice to the EAG was that this was unlikely. Therefore, the EAG implemented a symmetric approach to down-titration of dose. Ideally, it would have preferred to reduce the treatment effect and AE profile of vamorolone to mirror that in the SoC arm. However, the structure of the model prohibited this, therefore the EAG removed the impact of the reduction in dose on treatment effect and AE exposure in the SoC arm. In this scenario, as the total QALYs increased in both prednisone and deflazacort arms, owing to an increase in proportion on treatment, the incremental QALYs reduced thereby increasing the ICER (vamorolone vs prednisone) by 46%.

6.2.3. Applying an alternative SoC definition (prednisone and deflazacort proportions)

Clinical opinion to the EAG suggested that the split between prednisone and deflazacort in the UK is now nearer 50:50 (assumed as part of SoC; see Section 4.2.4 for more details), rather than the 85:15 assumed by the company. Therefore, the EAG conducted a scenario analysis with a 50:50 split to assess its impact on the cost effectiveness estimates. While drug costs were similar for prednisone and deflazacort, the two drugs varied in their safety profiles and the proportions of patients discontinuing in the long term. Because of this, the total QALYs were found to increase in SoC, leading to a reduction in the incremental QALYs gained for vamorolone and a 17% increase in the ICER. Note this scenario is incompatible with the EAG's preference for fully incremental analysis of discrete treatment strategies. The results are therefore presented in Table 40 (section **Error! Reference source not found.**).

6.2.4. Stopping treatment (for both vamorolone and SoC) at loss of ambulation

Clinical advice to the EAG indicated some uncertainty – in terms of real-world clinical practice – around the appropriate disease stage for stopping treatment, and indeed whether stopping was required at all. This was the case for both vamorolone and SoC. Although clinical advice indicated that stopping treatment at health state 6, as assumed in the company's base case, was not unreasonable, it was also confirmed that some clinicians may reasonably decide – in

consultation with patients and their families – to stop treatment at loss of ambulation. This scenario explored the impact of this uncertainty on the cost-effectiveness. It led to a reduction of 24% in the ICER, owing to reduced treatment costs because of early discontinuation (section **Error! Reference source not found.**).

6.2.5. Alternative rates of stunted growth and behavioural issues for vamorolone in the long term

The company assumed that people on vamorolone had zero stunted growth and – compared to SoC – a reduced incidence of behavioural issues. However, it was not clear in the company submission how the mechanism of action of vamorolone differs sufficiently from other glucocorticoids for such an assumption to be made. Therefore, EAG explored two scenarios 1) assuming that there would be small proportion of patients (5%) who would be experiencing stunted growth and behavioural issues in the long term with vamorolone 2) assuming that stunted growth and behavioural issues in the long term with vamorolone would be the same as SoC. While the smaller proportion assumption of 5% (1) was considered in the EAG base case, assuming to be the same as SoC (2) was considered as a scenario.

While assuming 5% events in the long term increased the ICER only by 4%, assuming it to be the same as SoC had tangible impact on the ICER (an increase of 24% was noted). This is due to the reduction in QALYs with vamorolone because of: disutility associated with stunted growth and behavioural issues, and the costs of growth hormone injections.

6.2.6. Excluding any additional mortality risk for patients over 30 years of age

In the company's base case, transition probabilities were modified for patients aged 30 and over from health states 8a and 8b to death, thereby applying a higher mortality risk to those patients. As this a deviation from the natural history model, the EAG explored the impact of excluding this additional mortality risk for patients aged 30 and over. An increase in total costs, life years and QALYs were noted across the treatment arms, with a net effect of a slight reduction of 5% in the ICER compared to the company's corrected base case (section **Error! Reference source not found.**).

6.2.7. Estimating vamorolone long-term discontinuation based on deflazacort and prednisone CINRG data

The company's base case used relatively short-term (<1 year) discontinuation data from trial for vamorolone, compared to the long-term (~14 years) discontinuation data available for SoC treatments based on CINRG. In contrast, the EAG base case assumed that vamorolone long-term discontinuation rates were the same as those seen for deflazacort (taken from the CINRG data) and extrapolated using a generalised gamma distribution beyond the observation period, as it was the distribution found to best fit the CINRG KM data. Deflazacort data was chosen for vamorolone discontinuation in the base case as their KM curves were found to be similar. There is also the expectation of better adherence to vamorolone versus prednisone owing to fewer side effects. As with the deflazacort CINRG data, the proportion on treatment in this scenario in the long term increased. The ICER increased substantially by 144%, mainly due to increase in vamorolone drug costs.

To explore further the uncertainty associated with this assumption, the EAG also implemented a scenario where vamorolone discontinuation data were assumed to be the same as prednisone (again based on the CINRG data). This scenario resulted in a proportion on treatment in the long term that was lower than that of deflazacort, but still higher than the vamorolone discontinuation rates (extrapolated using trial data) used in company base case. This resulted in increased treatment costs with vamorolone and an increased ICER of 73%.

6.2.8. Increased adverse events profile

The company included only moderate to severe adverse events in its estimate of the incidence of adverse events, despite all adverse events being defined as "severe and of sudden onset". The EAG therefore included the company's scenario including all adverse events in its analyses, in order to compare against the EAG corrected company base case.

6.2.9. Excluding carer QALYs

The company's modelled base case considered both patient and carer QALYs. In this scenario, the EAG explored the impact of not including carer QALYs. This was considered a useful scenario because of the uncertainty regarding the number of carers typically needed for a person with DMD, and the general lack of robust utility estimates. A substantial increase of 132% was observed in the ICER, as not considering carer QALYs resulted in a considerable reduction in incremental QALYs (section **Error! Reference source not found.**).

6.2.10. Using alternative health state utility values from the literature

This scenario explored the impact of alternative patient utility estimates (based on EQ-5D-3L) from Landfeldt (2023)[32] on the cost-effectiveness results. Landfeldt reported these values from an international cohort of patients,[33] where 58% of participants were from the United States or the United Kingdom (combined percentage reported in the paper). As the utilities for late ambulatory stages were relatively lower in Landfeldt, the total QALYs with the treatments reduced, resulting in a slight increase in QALY gain and a slight reduction in ICER (1%, section **Error! Reference source not found.**).

6.2.11. Excluding out-of-scope non-medical costs

The health state costs based on the BOI study in the company's base case included some out-of-scope non-medical costs. These included OTC medications, transport, alternative therapies, and transfer payments. The company's unit cost estimates for spinal surgery for scoliosis also included indirect costs. The EAG explored a scenario where these costs were excluded. Specifically, health state costs included all items in the CS (Table 67: Tests and medical procedures, medical devices, consultations and hospitalisations), plus only home alterations (from Table 68), based on the assumption that these would be paid for by social services. Indirect costs were excluded from the cost of treatment for scoliosis/spinal fusion surgery (last item of Table 72). Though a reduction in health-state related costs were noted in both treatment arms, the magnitude of reduction was higher with vamorolone. This is because more patients stayed in less severe, and therefore less costly, health states. This led to a slight reduction in incremental costs and a reduction of 1% in the ICER.

6.2.12. Excluding growth hormone costs for stunted growth

Clinical advice to the EAG suggested that growth hormone treatments are rarely used in DMD in the UK. Therefore, the EAG investigated the impact of excluding growth hormone therapy costs and included it in the preferred assumptions. As the adverse event costs reduced in the prednisone arm, an increase in incremental cost was noted, resulting in a 14% increase in the ICER (vamorolone versus prednisone). However, as AE costs substantially reduced for deflazacort, given that stunted growth is relatively more prominent in the deflazacort arm, the ICER for deflazacort versus prednisone reduced by 87% and it was no longer extendedly dominated by prednisone.

6.2.13. Using a 1x and 1.2x severity modifier

Based on the absolute QALY shortfall of [redacted] observed for prednisone and [redacted] observed for deflazacort in the EAG probabilistic base case (as given in Table 42, Reference case), a QALY modifier of 1.2x has been used in the EAG's base case. However, in this scenario, the EAG explores the impact of having no QALY modifier (i.e., a multiplicator of 1x) on cost-effectiveness. An increase of 47% in ICER was observed compared to company base case, owing to the reduction in incremental QALY gain with a lower QALY modifier.

6.2.14. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results of the EAG's exploratory and sensitivity analyses described above are provided in Table 39 and Table 40. Each change has been made individually and results are presented as fully incremental analyses, disaggregating the blended comparator of SoC into prednisone and deflazacort. Only deterministic analyses are presented, with both deterministic and probabilistic results presented for the EAG's preferred base case.

Table 39. EAG's exploratory analyses (deterministic)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)	% change from EAG corrected company base case
EAG corrected company base case						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Cohort starting age = 5 years						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13%
Symmetric impact of down-titration of treatment dose						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46%
Treatment stopping at loss of ambulation (based on clinical advice to EAG)						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-24%
Stunted growth and behavioural issues with vamorolone 5%						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4%
Stunted growth and behavioural issues with vamorolone same as SoC						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24%
No additional mortality risk for patients aged over 30 years						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-5%
Vamorolone discontinuation assumed to be the same as deflazacort (CINRG data)						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	144%
Vamorolone discontinuation assumed to be the same as prednisone (CINRG data)						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73%
Increased adverse events profile						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-97%
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19%
Exclude carer QALYs						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	132%
Alternative utility values (EQ-5D-3L) based on Erik Landfeldt, 2023[32]						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-1%
Exclude out-of-scope costs						

Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-1%
Exclude growth hormone costs						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-87%
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14%
QALY severity modifier = 1x						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47%
QALY severity modifier = 1.2x						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29%

Abbreviations: EAG, External Assessment Group; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 40. Alternative SoC definition (50% prednisone and 50% deflazacort)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	% change from EAG corrected company base case
EAG corrected company base case						
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC (85:15)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 50:50 (50% prednisone and 50% deflazacort)						
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18%
SoC (50:50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

6.3. EAG's preferred assumptions

The EAG incorporated the following assumptions for its preferred base case:

- Prednisone and deflazacort were considered as individual comparators with fully incremental analysis and the adverse event rates adjusted accordingly. The company base case used a blended SoC comparator.

- SoC patients on reduced dosages were assumed to remain at full SoC efficacy rather than reduced efficacy. This assumption was made to be consistent with the same assumption that had been made in the company base case for vamorolone (implemented by setting the proportion on 'full efficacy' following down titration to be the same as proportion on treatment in the 'Engine_2' sheet of the model). (Note it would have been preferable to apply a reduced effect to reduced dose for vamorolone to match SoC rather than the other way around but the model structure did not enable this).

- It was assumed that long-term rates of stunted growth and behavioural issues, experienced as moderate/severe AESI, would both be 5% for people on vamorolone. This was based on clinical advice to the EAG that patients might experience these side effects in later years. The company's base case assumed a rate of 0% for both.

- Vamorolone treatment discontinuation rates were assumed to be the same as deflazacort, based on long-term (approx. 14 years) CINRG data. Deflazacort data was chosen as its KM curve closely resembled that of vamorolone (based on EAP data presented in the clarification response) and because better adherence (versus prednisone) might be expected given the improved side effect profile claim for vamorolone. The company base case, however, used short-term trial data (48 weeks), subject to uncertainty beyond a year. Also, a generalised gamma parametric extrapolation of the proportion of patients discontinuing treatments in the long term was used as it fitted the KM curves of prednisone and deflazacort (based on CINRG data) more closely than the log-logistic used in the company's base case.

- Non-reference case health state and spinal fusion surgery cost items were excluded from the analysis.

- Growth hormone costs were excluded from the analysis on the basis of clinical opinion to the EAG.

- A QALY multiplier of 1.2x was used as the likely absolute QALY shortfall (based on the EAG base case) was observed to be between 12 to 18. The EAG also noted that there is uncertainty around the absolute QALY shortfall, as expected QALYs for the general population were based on EQ-5D-3L while QALYs for people living with DMD were derived using DMD-QoL (a disease specific QoL instrument).

The results of these changes, presented in Table 41, are shown both in terms of their isolated and collective impact.

Table 41. EAG's preferred base case assumptions (applied individually)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)
EAG corrected company base case					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symmetric impact of down-titration of treatment dose					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% stunted growth and behavioural issues with vamorolone in long-term					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation extrapolated using gen-gamma with vamorolone discontinuation assumed same as deflazacort CINRG data					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude out-of-scope costs					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude growth hormone costs					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.2x QALY multiplier applied					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (deterministic)					

Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (probabilistic)					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

6.4. Conclusions of the cost-effectiveness section

Based on the EAG's preferred assumptions in the base case, in boys with DMD aged 4 and older, vamorolone resulted in a fully incremental ICER of [redacted]. This is calculated from an additional cost of [redacted] over deflazacort, for a QALY gain of [redacted] (over a 50-year time horizon), in the deterministic analysis at the PAS price. The probabilistic analysis resulted in a similar QALY gain ([redacted]) for an additional cost of [redacted] resulting in an ICER of [redacted]. Both figures are substantially higher than the willingness-to-pay threshold of £30k/QALY. Therefore, vamorolone is not likely to be a cost-effective treatment option for this population based on the current PAS and EAG's model assumptions.

The key drivers of cost-effectiveness were:

- treatment discontinuation of vamorolone in the longer-term,
- efficacy assumptions following down-titration or dose reduction of treatments,
- the long-term safety profile of vamorolone, especially related to stunted growth and behavioural issues,
- whether carer QALYs are considered, and
- the severity modifier (1.7 or 1.2) applied.

The EAG considered that the company's model structure, based on project HERCULES, adequately captured disease progression via the health states modelled. However, the EAG was concerned about the blended comparison of prednisone and deflazacort (versus vamorolone) as it prevented evaluation of interventions along the efficient frontier. To enable a fully incremental analysis, and to capture the distinct safety profiles of prednisone and deflazacort, the EAG preferred distinct comparison with the two separate SoC treatments.

Furthermore, the key assumptions driving the model – especially those related to treatment effectiveness and discontinuation – were associated with high uncertainty. This was reflected through a substantial increase in the ICER (versus the company's base case) when the EAG's preferred assumptions were implemented. While several EAG scenarios explored uncertainties around the company's modelled analyses, these should only be seen as a starting point towards addressing those uncertainties.

Finally, the QALY shortfall, calculated for current SoC treatments based on EAG's analyses, indicated that 1.2x should be applied as a disease severity modifier. This contrasted with the company's use of a 1.7x modifier.

7. QALY MODIFIER

NICE's severity modifier considers disease severity based on QALY shortfall. Inputting the EAG base case probablistic results into the Schneider et al. QALY Shortfall Calculator[34], the shortfall value qualifies for a disease severity multiplier of 1.2x. For the EAG base case deterministic analysis, the QALY shorfall is slightly higher, but still within the 1.2x multiplier range. Application of the EAG deterministic scenarios for mortality risk (for patients aged 30 and over) and a 50:50 prednisone/deflazacort split (for SoC) decreased the QALY shortfall slightly, though remainig within the range meeting the 1.2x criteria.

The original company model showed a QALY shortfall of slightly more than 18 ([redacted]). Hence the 1.7x multiplier was applied. The company's updated model, following clarification and EAG corrections (as per Section 6.1), revealed a slightly reduced QALY shortfall of [redacted].

On the other hand, the proportional QALY shortfall from the EAG's base case did not meet the threshold for applying a QALY weight of 1.2, as it was found to be less than 0.85.

Table 42 below provides a summary of the QALY shortfall analysis using the EAG base case (probabilistic) for reference case, as well as alternative cases or value sets. In all cases, the absolute QALY shortfall was found to be less than 18, and the proportional QALY shortfall was found to be less than 0.85.

Table 42. QALY shortfall analysis using EAG base case assumptions

Schneider shortfall calculator	Expected total QALYs for general population	Total QALYs (DMD-QoL) that people living with a condition would be expected to have with current treatment	QALY shortfall
Reference case: MVH value set + HSE 2014 ALDVMM model			
Prednisone	24.90	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Deflazacort	24.90	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Alternative A: 5L to 3L mapping (Hernandez Alava et al) + HSE 2017-18			
Prednisone	24.08	[redacted]	Absolute shortfall: [redacted]

Schneider shortfall calculator	Expected total QALYs for general population	Total QALYs (DMD-QoL) that people living with a condition would be expected to have with current treatment	QALY shortfall
			Proportional shortfall: [redacted]
Deflazacort	24.08	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Alternative B: 5L to 3L mapping (van Hout et al) + HSE 2017-18			
Prednisone	24.07	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Deflazacort	24.07	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Alternative C: MVH value set + health state profiles			
Prednisone	24.66	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Deflazacort	24.66	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Alternative D: MVH value set + HSE 2012-14			
Prednisone	24.94	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Deflazacort	24.94	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]

Abbreviations: EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level; HSE: Health Survey for England; MVH: Measuring and Valuing Health; QALYs, quality adjusted life-years; DMD-QoL, Duchenne Muscular Dystrophy Quality of Life Measure

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Single Technology Appraisal

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

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 Monday 18 December 2023** 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 [redacted] should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Vamorolone efficacy

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17 states: "Prednisone 0.75 mg/kg/day was consistently more effective than vamorolone 6.0 mg/kg/day for the efficacy outcomes reported"	This text should be amended to: "Prednisone 0.75 mg/kg/day was consistently numerically superior compared to vamorolone 6.0 mg/kg/day for the efficacy outcomes reported but was not statistically significantly superior except for TTCLIMB and elbow flexor muscle strength.[1]"	It is misrepresentative to state that vamorolone is not as effective as prednisone in slowing down disease progression in muscle function since there is a lack of statistical significance in differences in almost all endpoints between vamorolone and prednisone.[1] Furthermore, when looking at baseline characteristics patients in the vamorolone 6.0 mg/kg arm had more severe disease based on baseline TTSTAND, 6MWT, NSAA and TTRW velocity outcomes than the prednisone arm; these baseline differences should be taken into account when assessing numerical differences. Therefore, the two treatments can be viewed as equally effective. Vamorolone 6.0 mg/kg achieved minimal clinically important differences when compared to placebo at 24 weeks for TTSTAND, 6MWT, TTRW, TTCLIMB, and NSAA; these differences were maintained to 48 weeks.[1,2] This indicates	The EAG does not consider this to be a matter of factual inaccuracy. As stated in the report, the benefit of prednisone 0.75 mg/kg/day over vamorolone 6.0 mg/kg/day was close to the MCID for the primary outcome, TTSTAND, and in excess of the MCID for TTCLIMB velocity. The benefit was statistically significant for TTCLIMB and elbow flexor muscle strength, with a numerical benefit for all other clinical outcomes reported. Therefore, the EAG consider it appropriate to state that prednisone 0.75 mg/kg/day was consistently more effective than vamorolone 6.0 mg/kg/day.

		that patients receiving vamorolone 6.0 mg/kg would receive clinically meaningful improvements in their condition.	No change has been made to the EAR.
Page 61 states: "Prednisone was more effective than vamorolone at either 2.0 or 6.0 mg/kg/day"	This text should be amended to: "Prednisone was statistically significantly superior compared to vamorolone 2.0 mg/kg/day and numerically superior compared to vamorolone 6.0 mg/kg/day for the efficacy outcomes reported but was not statistically significantly superior except for TTCLIMB and elbow flexor muscle strength[1]"		The EAG does not consider this to be a matter of factual inaccuracy. As stated above, prednisone 0.75 mg/kg/day was numerically more effective than vamorolone at both the 6.0 mg/kg/day dose and the 2.0 mg/kg/day dose for all clinical outcomes reported. For the 6.0 mg/kg/day dose this difference was statistically significant for two of seven clinical outcomes reported. For the 2.0 mg/kg/day dose this difference was statistically significant for four of seven clinical outcomes reported. No change has been made to the EAR.

Page 69 states: "The EAG disagreed with the company somewhat – while it concluded that there was no clear evidence that treatment outcomes reduced after switching from prednisone to vamorolone, the evidence nevertheless suggested that this was possible. Given evidence that prednisone may outperform vamorolone for clinical outcomes, the EAG considered it plausible that longer follow-up data would show a reduction in treatment effect following a switch from prednisone to vamorolone 0.6 mg/kg/day."	The text should be amended to: "The EAG disagreed with the company somewhat – while it concluded that there was no clear evidence that treatment outcomes reduced after switching from prednisone to vamorolone, the evidence nevertheless suggested that this was possible. The EAG considered it plausible that longer follow-up data would show a reduction in treatment effect following a switch from prednisone to vamorolone 6.0 mg/kg/day, despite there being no clear evidence of this."		
Page 79 states: "On the balance of probabilities, the EAG considered it likely that	This text should be amended to: "Despite there being no clear evidence to support		The EAG does not consider this to be a matter of factual inaccuracy. The statement referenced constitutes EAG's interpretation of the

vamorolone would not be as effective as prednisone in slowing down disease progression in muscle function."	it, the EAG considered it possible that vamorolone would not be as effective as prednisone in slowing down disease progression in muscle function."		evidence presented in the CS. No change has been made to the EAR.
The EAG expressed a preference for seeing efficacy outcomes for vamorolone versus standard of care (SoC) options beyond 24-weeks. A comparison of VISION-DMD and FOR-DMD is available, and safety outcomes from this comparison were presented in Section B.2.9 of the original company submission. While it is acknowledged that it does not constitute a factual inaccuracy, as the EAG has expressed a preference for seeing efficacy outcomes, results of the efficacy comparison are presented here. Outcomes are presented for the 24-week (6-month) and 48-week (12-month) timepoints and presented for vamorolone 6 mg/kg/day (VISION-DMD) versus prednisone 0.75 mg/kg/day and deflazacort 0.9 mg/kg/day (both FOR-DMD). Analyses were conducted using the modified intent-to-treat set 2 (mITT-2), which included all subjects who received at least one dose of study treatment and had a postbaseline efficacy assessment in VBP15-004 Treatment Period 2[3]. Comparisons of vamorolone 6 mg/kg/day against prednisone and deflazacort are		The population-matched comparison of the VISION-DMD vs. FOR-DMD studies show that for the primary endpoint time to stand from supine (TTSTAND) velocity, vamorolone 6 mg/kg/day and prednisone 0.75 mg/kg/day were [redacted]. The numerical differences were [redacted] Consistently, similar results were observed at 12 months with even smaller numerical differences, in this case [redacted].	As acknowledged by the company, this is not a matter of factual inaccuracy. The EAG thank the company for undertaking further indirect analysis of the vamorolone 6 mg/kg/day arm of the VISION-DMD trial with the prednisone 0.75 mg/kg/day and deflazacort 0.9 mg/kg/day arms in the FOR-DMD trial. No change has been made to the EAR.

reported for all available efficacy endpoints in the ‘Justification for amendment’ column.	[redacted] For 6-minute walk test (6MWT) distance, vamorolone 6 mg/kg/day and prednisone 0.75 mg/kg/day differences [redacted]. A similar result was observed for the comparison vs. deflazacort 0.9 mg/kg/day [redacted] For time to run/walk 10m (TTRW) velocity distance, vamorolone 6 mg/kg/day and prednisone 0.75 mg/kg/day differences were [redacted]. A similar result was observed for the comparison vs. deflazacort 0.9 mg/kg/day	

	[redacted] For North Star Ambulatory Assessment (NSAA) score, vamorolone 6 mg/kg/day and prednisone 0.75 mg/kg/day were [redacted] was observed between vamorolone 6 mg/kg and deflazacort 0.9 mg/kg/day at 6 months [redacted] At month 12, [redacted] The comparison of VISION-DMD to FOR-DMD suggests that the prednisone arm in the VISION-DMD study performed unusually well as can be concluded by the lower numerical efficacy observed in prednisone and deflazacort in the FOR-DMD study. This is in line with	

	the imbalance at baseline within VISION-DMD, suggesting a less severe population in the prednisone arm of the VISION-DMD study than any other arm of the VISION-DMD or the FOR-DMD study.	

Issue 2 QALY severity multiplier

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The Company consider that the 1.2x modifier applied by the EAG is incorrect, as according to the NICE manual for health technology evaluations vamorolone is eligible for the 1.7x modifier.	The Company request that the EAG applies the 1.7x modifier in their preferred base case.	Using the original CS model in the Schneider QALY Shortfall Calculator leads to a QALY shortfall of [redacted], a proportion shortfall of 72.37%, and 6.88 remaining QALYs with the disease.[4] This produces a QALY weight of 1.7x. Based on amendments described in issues 1, 3, 5, and 7, applying the SoC QALYs from the EAG model ([redacted]) to the QALY Shortfall Calculator	The EAG does not consider this to be a matter of factual inaccuracy. The absolute QALY shortfall in the EAG preferred base case was [redacted] for prednisone and [redacted] for deflazacort in the reference case, as indicated in Table 42 of the EAG report. These shortfall values clearly fall within the range of 12-18, which is the

		gives a QALY shortfall of [redacted], a proportional shortfall of 72.25%, and a QALY weight of 1.2x. The absolute shortfall falls on the cut-off between severity levels for 1.2x and 1.7x. Given the uncertainty around the modifier and the likelihood of the QALY shortfall falling on the cut-off between severity levels of an absolute QALY shortfall of 18.00 years, the higher severity level of 1.7x should apply, as per the NICE manual for health technology evaluations.[5]	qualifying criteria for the 1.2x modifier. No change has been made to EAR.
Pages 14 and 22 state: "The company used a 1.7x QALY severity multiplier in the model, while the EAG believed that a 1.2x multiplier was more appropriate."	This text should be amended to: "The company used a 1.7x QALY severity multiplier in the model, which the EAG agrees is an appropriate modifier."		This is not a factual inaccuracy. No change has been made to EAR.
Page 114 states: "Finally, the QALY shortfall, calculated for current SoC treatments based on EAG's analyses, indicated that 1.2x should be applied as a disease severity modifier. This contrasted with the company's use of a 1.7x modifier."	This text should be amended to: "Finally, the QALY shortfall, calculated for current SoC treatments based on EAG's analyses, falls on the cut-off between severity levels for 1.2x and 1.7x and therefore the 1.7x modifier should be used, as per the NICE manual for health technology evaluations.[5]"		This is not a factual inaccuracy. No change has been made to EAR.
Page 22 states: "Given the high uncertainty around the modifier and the	This text should be amended to: "Given the uncertainty around the modifier and the likelihood of the QALY		This is not a factual inaccuracy. No change has been made to EAR.

likelihood of QALY shortfall falling between 12-18 years in the EAG base case, a QALY multiplier of 1.2x was considered."	shortfall falling on the cut-off between severity levels of an absolute QALY shortfall of 18 years, the higher severity level of 1.7x should apply, as per the NICE manual for health technology evaluations.[5]"		
Page 106 states: "Based on the absolute QALY shortfall of [redacted] as per the EAG base case, a QALY modifier of 1.2x has been used in the EAG's base case."	This text should be amended to: "Based on the absolute QALY shortfall of [redacted] as per the amended EAG base case, a QALY modifier of 1.7x has been used in the EAG's base case"		EAG noted a copy-paste error in the absolute QALY shortfall value in page 106 and so the text has been corrected in the EAR, page 106 as below: "Based on the absolute QALY shortfall of [redacted] observed for prednisone and [redacted] observed for deflazacort in the EAG probabilistic base case (as given in **Error! Reference source not found.**, Reference case), a QALY modifier of 1.2x has been used in the EAG's base case."

Page 110 states: "A QALY multiplier of 1.2x was used as the likely absolute QALY shortfall (based on the EAG base case) was observed to be between 12 to 18."	This text should be amended to: "A QALY multiplier of 1.7x was used as the likely absolute QALY shortfall (based on the amended EAG base case) was observed to be between 17.99 to 18.02."		This is not a factual inaccuracy. No change has been made to EAR.

Issue 3 Use of a blended comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19 states: "Clinical expert opinion to the EAG was that, in clinical practice in the NHS, there was an approximately 50/50 split in the use of prednisone and deflazacort."	This text should be amended to: "A recent study of the socioeconomic cost of DMD in the UK published in 2020 found there was an approximately 85/15 split in the use of prednisone and deflazacort. However, clinical expert opinion to the EAG was that, in clinical practice in the NHS, there was an approximately 50/50 split in the use of prednisone and deflazacort.[6]"	The 85:15 split originally used in the model is from a recent study of the socioeconomic cost of DMD in the UK published in 2020.[6] As such, the published split of comparator therapies is the most appropriate reference to use throughout. Treatment guidelines suggest the use of glucocorticoids, but there are no set guidelines for which specific glucocorticoids to use for the treatment for DMD patients. Therefore, the	The EAG does not consider this to be a matter of factual inaccuracy. As stated in the report, clinical expert opinion to the EAG was that, in clinical practice in the NHS, there was an approximately 50/50 split in the use of prednisone and deflazacort in new patients. The company's estimate was taken from a survey of neuromuscular

		rationale for the SoC arm is to include both of the current treatments for DMD and base usage on the most up to date published data.	specialists in 2020, who offered a historical sample of corticosteroid treatment of people with DMD. No change has been made to the EAR.
Page 87 states: "Clinical opinion to the EAG was that both prednisone and deflazacort were considered standard of care in the UK, however the proportion of new patients receiving each treatment was approximately 50/50."			This is not a factual inaccuracy. No edit made.
Page 19 states: "Where possible within the current model framework, the EAG compared vamorolone to each corticosteroid separately."	This text should be amended to: "Where possible within the current model framework, the EAG compared vamorolone to each corticosteroid separately, despite a lack of efficacy data split by each SoC comparator."	There was a lack of separate efficacy data split by each SoC comparator, prednisone and deflazacort, hence this caveat should be added. Additionally, a key finding of the FOR-DMD study was that prednisone and deflazacort can be considered equally efficacious, further reducing	This is not a factual inaccuracy. The EAG highlighted the issues with data in Section 4.2.6. No change has been made to the EAR.
Page 19 states: "The EAG therefore conducted a scenario	This text should be amended to: "The EAG therefore conducted a scenario analysis using a blended		This is not a factual inaccuracy. No change

analysis using a blended comparator treatment split of 50% prednisone and 50% deflazacort, though, overall, retained its preference for separate comparators."	comparator treatment split of 50% prednisone and 50% deflazacort, though, overall, retained its preference for separate comparators, despite a lack of efficacy data split by each SoC comparator."	the need to consider prednisone and deflazacort separately.	has been made to the EAR.
Page 113 states: "To enable a fully incremental analysis, and to capture the distinct safety profiles of prednisone and deflazacort, the EAG preferred distinct comparison with the two separate SoC treatments."	This text should be amended to: "To enable a fully incremental analysis, and to capture the distinct safety profiles of prednisone and deflazacort, the EAG preferred distinct comparison with the two separate SoC treatments, despite a lack of efficacy data split by each SoC comparator."		This is not a factual inaccuracy. No change has been made to the EAR.

Issue 4 ICERs only presented as part of fully incremental analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG presents a fully incremental analysis of vamorolone, prednisone and deflazacort. As deflazacort is extendedly dominated in most	To display ICERs for all scenarios shown for vamorolone versus prednisolone and deflazacort separately, in addition to the fully incremental analysis presented in the current report.	In splitting the SoC arm into separate comparators (see Issue 3), the EAG consider the distinction between prednisone and deflazacort to be sufficiently important to	The EAG considers deflazacort, prednisone and vamorolone to be distinct treatment options. Therefore, they should be analysed as

scenarios, the ICER for vamorolone is most often versus prednisone only. However, as deflazacort is used in practice it is relevant to also present results of vamorolone versus prednisone and vamorolone versus deflazacort separately.		assess the cost-effectiveness of vamorolone separately for each comparator. However, in presenting an incremental analysis only, the cost-effectiveness of vamorolone is only ever assessed versus one comparator. FOR-DMD found no difference in efficacy between prednisone and deflazacort, and therefore it is appropriate to compare them as one to vamorolone. The use of a blended comparator as per the original company submission allows comparison to both comparators, which is appropriate given that both prednisone and deflazacort are used in practice. The result of the EAG's current approach is that the cost-effectiveness of vamorolone is misrepresented, as results tend to only be presented versus the most cost-effective	such in a fully incremental analysis. No change has been made to the EAR.
Page 103 states: "the incremental QALYs reduced thereby increasing the ICER (vamorolone vs prednisone) by 46%"	This text should be amended to: "the incremental QALYs reduced thereby increasing the ICER (vamorolone vs prednisone) by 46%, and increasing/decreasing the ICER (vamorolone vs deflazacort) by XX%." With the EAG inputting the relevant percentage here.		The analysis is a fully incremental analysis, therefore the two-way comparison with deflazacort is not relevant. No change has been made to the EAR.

		comparator in each scenario, thereby presenting a higher ICER for vamorolone in each scenario.	

Issue 5 Proportion of vamorolone patients experiencing AEs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15 states: "The EAG preferred to assume that a small proportion of patients on vamorolone (10% for All AESI and 5% for moderate/severe AESI) will experience stunted growth and 5% will experience behavioural issues as moderate/severe AESI."	The text should be amended to: "The EAG, based on clinical opinion, preferred to assume that a moderate proportion of patients on vamorolone (10% for All AESI and 5% for moderate/severe AESI) will experience stunted growth and 5% will experience behavioural issues as moderate/severe AESI as a pessimistic arbitrary assumption."	The only rationale provided for the values of 10% and 5% assumed for all AESI and moderate/severe AESIs is based on clinical opinion and not clinical trial data, hence these are arbitrary values determined by the EAG. Growth stunting was seen with [redacted] during the first [redacted] of treatment, but it was [redacted] Additionally, this [redacted] of [redacted] seen with [redacted] was	The EAR was clear that these estimates are based on clinical opinion (as mentioned in Key issue 6, Section 3.2.3 and 4.2.6). No change has been made to the EAR.
Page 21 states: "The EAG opted to assume that a small proportion of patients on vamorolone	The text should be amended to: "The EAG, based on clinical opinion, opted to assume that a moderate proportion of patients on vamorolone		Not a factual inaccuracy. No change has been made to the EAR.

(10% for All AESI and 5% for moderate/severe AESI) will experience stunted growth and 5% will experience behavioural issues as moderate/severe AESI."	(10% for All AESI and 5% for moderate/severe AESI) will experience stunted growth and 5% will experience behavioural issues as moderate/severe AESI as a pessimistic arbitrary assumption."	rescued following the [redacted] to either [redacted] in the subsequent [redacted] period of evaluation.[6] As such, the 5% and 10% proportions assumed for stunted growth AESIs are grossly overestimated by the EAG.	
Page 110 states: "It was assumed that long-term rates of stunted growth and behavioural issues, experienced as moderate/severe AESI, would both be 5% for people on vamorolone. This was based on clinical advice to the EAG that patients might experience these side effects in later years."	The text should be amended to: "It was assumed that long-term rates of stunted growth and behavioural issues, experienced as moderate/severe AESI, would both be 5% for people on vamorolone. This was based on clinical advice to the EAG that patients might experience these side effects in later years, but remains a pessimistic, arbitrary value assumed by the EAG."		Not a factual inaccuracy. No change has been made to the EAR.

Issue 6 Average starting age in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 86 states: "It was not clear why the company opted to use Vry et al. to derive baseline age,	This text should be amended to: "The company used Vry et al. to derive the baseline age of patients in the model since the paper presents the	As stated in the original CS, Vry et al. presents the average age at diagnosis of DMD in the UK and	The EAG does not consider this to be a matter of factual inaccuracy. The EAG

as opposed to the pivotal trial (VISION DMD).”	average age at diagnosis of DMD in the UK.[7]”	represents a robust source from which to obtain the average starting age in the model.[7]	understands that children with DMD are not necessarily treated with glucocorticoids at diagnosis, and that treatment begins when a child’s motor skills have stopped improving but have not yet begun to decline. Children recruited to VISION-DMD were naive to glucocorticoid treatment but were eligible to start treatment. Therefore, the EAG consider the baseline age of children in VISION-DMD to better represent the average starting age of children in model than age at diagnosis. No change has been made to the EAR.

Issue 7 Discontinuation parametric curve choice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20 states: "The EAG considered generalised gamma to be best fitting curve for SoC."	Text should be amended to; "The EAG considered log-logistic to be an appropriate curve for SoC and the generalised gamma to be the most conservative curve for SoC."	The generalised gamma curve has a long tail that could overestimate the number of patients receiving SoC and therefore does not represent the best fitting curve, rather it is the most conservative curve. As stated in the clarification question response, considering model fit based on AIC/BIC values, all curves fit the prednisone data similarly well, and all curves except for exponential fit the deflazacort data reasonably well. In line with recommendations from Technical Support Document 14, the log-logistic model was applied to both the prednisone and deflazacort arms for consistency with the vamorolone arm.	The EAG does not consider this a factual inaccuracy. Generalised gamma had the lowest AIC/BIC values for deflazacort (chosen discontinuation data for the EAG base case) and also aligned closely with CINRG KM data as well as the vamorolone EAP KM curve. No change has been made to the EAR.

Issue 8 Data selection for vamorolone discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Use of deflazacort CINRG data to model vamorolone discontinuation despite EAG questioning the validity of the deflazacort discontinuation data	The company request that the EAG present an alternative scenario considering the prednisone discontinuation curve from CINRG, given the EAG's critique of the deflazacort curve	The EAG's approach to modelling vamorolone discontinuation is extremely conservative and is counterintuitive when the EAG also query the validity of the deflazacort curve. The EAG criticise the deflazacort discontinuation curve as lacking face validity, however, use this to model vamorolone discontinuation in the base case. If the EAG have concerns with the deflazacort discontinuation curve, the company consider it more appropriate to model the vamorolone discontinuation curve given this is based on actual vamorolone data, or model the prednisone CINRG curve given this is the most mature of the three Kaplan-Meier curves.	The EAG does not consider this a factual inaccuracy. Also, the alternative scenario of considering the prednisone discontinuation curve from CINRG was presented in the EAR, Table 39, with the scenario description in Section 6.2.7. EAG would like to clarify that the deflazacort discontinuation curve was not selected because it was ideal, but because it was the closest possible approximation available for vamorolone discontinuation. (The EAG noted that the deflazacort CINRG KM curve visually matched

		The EAG's preferred assumption to use deflazacort discontinuation data from CINRG for the discontinuation of vamorolone therefore represents a highly conservative approach, and text should be amended to reflect this.	closely that of the vamorolone EAP KM curve provided in the company's clarification response, Figure 6). CINRG data was unavailable, and so the EAG was unable to do anything with its limitations. No change has been made to the EAR.
Page 20 states: "The company's method for extrapolating these short-term data provided some advantage for vamorolone in the model"	This text should be amended to: "The company's method for extrapolating these short-term data conservatively included the efficacy of discontinued patients and provided some advantage for vamorolone in the model"	Discontinuation data in the model affects the efficacy data. Since the modified ITT analysis was used for the efficacy of vamorolone and SoC, the efficacy of discontinued patients is implicitly included in the efficacy data for vamorolone and SoC. The base case analysis can be considered conservative as this assumes loss of efficacy upon discontinuing and therefore possibly underestimates the efficacy of vamorolone. This	This is not a factual inaccuracy. No change has been made to the EAR.
Page 20 states: "The EAG assumed that the proportion of patients discontinuing vamorolone would be the same as CINRG data for deflazacort in the long term."	This text should be amended to: "The EAG assumed a highly conservative approach that the proportion of patients discontinuing vamorolone would be the same as CINRG data for deflazacort in the long		This is not a factual inaccuracy. No change has been made to the EAR.

	term, since vamorolone has a better safety profile compared to deflazacort."	conservative approach is not acknowledged by the EAG currently.	
Page 104-105 states: "The company's base case used relatively short-term (<1 year) discontinuation data from trial for vamorolone, compared to the long-term (~14 years) discontinuation data available for SoC treatments based on CINRG"	This text should be amended to: "The company's base case used relatively short-term (<1 year) discontinuation data from trial for vamorolone, compared to the long-term (~14 years) discontinuation data available for SoC treatments based on CINRG. This method conservatively included the efficacy of discontinued patients."		This is not a factual inaccuracy. No change has been made to the EAR.
Page 105 states: "the EAG base case assumed that vamorolone long-term discontinuation rates were the same as those seen for deflazacort"	This text should be amended to: "the EAG base case assumed a highly conservative approach that vamorolone long-term discontinuation rates were the same as those seen for deflazacort"		This is not a factual inaccuracy. No change has been made to the EAR.
Page 110 states: "Vamorolone treatment discontinuation rates were assumed to be the same as deflazacort, based on long-term (approx. 14 years) CINRG data"	This text should be amended to: "Vamorolone treatment discontinuation rates were highly conservatively assumed to be the same as deflazacort, based on long-term (approx. 14 years) CINRG data"		This is not a factual inaccuracy. No change has been made to the EAR.

Issue 9 Corrected base case ICER results cannot be replicated

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 111; Table 41: The ICER results for the EAG corrected company base case ICER cannot be replicated in the model provided. The subsequent ICERs included the EAG's preferred assumptions and the EAG cumulative base case ICER also cannot be replicated.	ICER results to be updated based upon the model provided. For example, the EAG's corrected company base case is [redacted] in the EAG's model. Subsequent ICERs to be updated based upon this amendment. As per the model, the following ICERs in isolation (with corrected base case) are stated below.	The EAG's provided model offers both a macro button to set the model to the EAG corrected company base case and a static description of the results. Both of these options present the resulting ICER of [redacted]. Replicating the corrected base case changes into the company's original model also produced the same results. The company is not able to replicate the ICERs provided within the EAG report which are substantially higher than those resulting from the model provided by the EAG. These results also have a subsequent impact on the probabilistic ICER. The company request that the EAG clarifies how these ICERs were obtained and update either the model or	The EAG reviewed the model and was able to replicate the results as per Table 41. The EAG notes that these results represent the fully incremental analyses reported in the 'Fully incremental results' sheet in the Excel model. The EAG would be happy to meet with the company to review if desired. To make the description in the report clearer, the EAG has made the following amendment to Section 6.3. "Prednisone and deflazacort were considered as individual comparators with fully incremental analysis and

		the report to ensure accurate results are reflected in both materials.	the adverse event rates were adjusted accordingly. The company base case used a blended SoC comparator.”

Issue 10 EAG preferred base case ICER results cannot be replicated

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 112; Table 41: The ICER results for the “Cumulative EAG base case results (deterministic)” could not be replicated within the model provided. [redacted]	This text should be amended to: [redacted]All subsequent ICERs in Table 41 should be updated to reflect the correct ICER.	The EAG’s provided model offers a macro button to set the model to the EAG’s base case (cumulative) inclusive of the 5 assumptions outlined in the EAG report. When selecting the macro, or manually amending the switches throughout the model to the same assumptions, the ICER presented is [redacted]however when manually corrected to include comparator percentages, the resulting ICER is [redacted] This value is lower than the [redacted]	The EAG has reviewed the model and was able to replicate the results as per Table 41. The EAG would be happy to meet with the company to review if desired. However, while checking these results, the EAG noted a minor coding error in its model which impacted scenarios 11, 12 and 13, which was

		ICER presented in the EAG report. Additionally, the [redacted]ICER is only obtained when selecting 100/0 deflazacort/prednisone in cells C64:C68 in the 'Cost data' sheet. When selecting 100/0 prednisone/deflazacort using the same cells, the resulting ICER is [redacted] As in Issue 9, this also has a subsequent impact on the probabilistic ICER. The company request that the EAG clarifies how these ICERs were obtained and update either the model or the report to ensure accurate results are reflected in both materials.	subsequently corrected in the model. An updated model has been included as part of EAG's FAC response. In the EAR, Table 40, a percentage change from the EAG corrected company base case was corrected to 18% (previously 17%).

Issue 11 One-way sensitivity analysis justification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 98 states: "No justification was provided for selecting the relatively short list of model input parameters."	This text should be amended to: "The top ten most sensitive model parameters were displayed in the OWSA table and figure."	As stated in the original CS, the top ten most sensitive parameters were presented in the OWSA results.	The EAG notes that the OWSA did not include all parameters, specifically the cost of vamorolone. The EAG's own analysis suggested that the ICER

			is highly sensitive to this and is therefore likely in the top 10 most sensitive parameters.

Issue 12 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 39 states "The company presented only methodological information about the VBP-15-002 and VBP-12-003 trials, and no results were reported in the CS"	This text should be amended to: "The company presented methodological information about VBP-15-002 and VBP-12-003 trials in the main CS, with summary of results presented in appendices."	This is factually inaccurate. As per the NICE template, given that these studies were not used within the economic model, results are not required in the main submission document. To aid clarity on the benefits of vamorolone, key results were presented within the appendices.	Thank you for this comment, the EAG agree that a summary of results of VBP-15-002 and VBP-12-003 were presented in Appendix L. The report has been edited as suggested by the company.

Page 69 states: "Given evidence that prednisone may outperform vamorolone for clinical outcomes, the EAG considered it plausible that longer follow-up data would show a reduction in treatment effect following a switch from prednisone to vamorolone 0.6 mg/kg/day."	This text should be amended to: "Given evidence that prednisone may outperform vamorolone for clinical outcomes, the EAG considered it plausible that longer follow-up data would show a reduction in treatment effect following a switch from prednisone to vamorolone 6.0 mg/kg/day."	Vamorolone 0.6 mg/kg/day is not a dosage used within the submission document. The EAG are referring to vamorolone 6.0 mg/kg/day.	Thank you for this correction. The report has been edited as suggested by the company.

Issue 13 Referencing errors

Location of error	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 30	Spelling of "Perrera" should be corrected to "Perera".	Spelling error in lead author's name.	Thank you for this correction. The report has been edited as suggested by the company.
Page 50 Missing references in Table 9 for VISION-DMD Phase 1 (24 weeks), VISION DMD Phase 1 and 2 (48 weeks) and VBP15-LTE trials	Include reference for VISION-DMD Phase 1 (24 weeks) – Guglieri M, Clemens PR, Perlman SJ, et al. Efficacy and Safety of Vamorolone vs Placebo and Prednisone Among Boys With Duchenne Muscular	To align with sources used in the original submission.	Thank you for this update. The report has been edited as suggested by the company.

	Dystrophy: A Randomized Clinical Trial. JAMA Neurol 2022. 79: 1005–1014. Include reference for VISION-DMD Phase 1 and 2 (48 weeks) – Hoffman E, Dang UJ, Damsker JM, et al. DRAFT Efficacy and safety of vamorolone over 48 weeks in a randomized, double-blind trial in Duchenne muscular dystrophy. Neurology 2023. Draft. Include reference for VBP15-LTE – Mah JK, Clemens PR, Guglieri M, et al. Efficacy and Safety of Vamorolone in Duchenne Muscular Dystrophy: A 30-Month Nonrandomized Controlled Open-Label Extension Trial. JAMA Netw Open 2022. 5: e2144178.		
Page 77 Section 3.3 paragraph one, when referring to VBP15-LTE, is incorrectly referring another trial.	The correct reference should be “Mah JK, Clemens PR, Guglieri M, et al. Efficacy and Safety of Vamorolone in Duchenne Muscular Dystrophy: A 30-Month Nonrandomized Controlled Open-Label		Thank you for this correction. The report has been edited as suggested by the company.

	Extension Trial. JAMA Netw Open 2022. 5: e2144178.”		
Page 89 Missing reference from text “Natural history transition probabilities in the HERCULES model”	HERCULES reference should be included “Broomfield J, Hill M, Chandler F, Crowther MJ, Godfrey J, Guglieri M, et al. Developing a Natural History Model for Duchenne Muscular Dystrophy. Pharmacoecon Open. 2023.”		The Broomfield (2023) citation has been cited as the HERCULES model on pages 85 and 88. No change has been made to the EAR.

Issue 14 Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 69	The original company submission was marked as confidential (page 64-65), as this text relates to describing figures marked as confidential. However, similar text was not marked up.	Add markup as was done in the original company submission to the text “treatment benefits seen with prednisone at Week 24 were maintained up to Week 48”. Similarly, text stating ‘levelled off’ between week 24 and week 48, with no further improvement in either arm. A small decrease in treatment	Thank you for noting incorrect marking. The report has been edited as suggested by the company.

		outcome between weeks 24 and 48".	

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(2) Hoffman, E.; Dang, U. J.; Damsker, J. M.; Guglieri, M.; Clemens, P.; Perlman, S. J.; Smith, E. C.; Horrocks, I.; Finkel, R.; Mah, J. K.; Deconinck, N.; Goemans, N.; Haberlova, J.; Straub, V.; Mengle-Gaw, L. J.; Schwartz, B. D.; Harper, A. D.; Shieh, P. B.; De Waele, L.; Castro, D.; Yang, M. L.; Ryan, M. M.; McDonald, C.; Tulinius, M.; Webster, R.; McMillan, H. J.; Kuntz, N. L.; Rao, V. K.; Baranello, G.; Spinty, S.; Childs, A.-M.; Sbrocchi, A. M.; Selby, K. A.; Monduy, M.; Nevo, Y.; Vilchez-Padilla, J. J.; Nascimento-Osorio, A.; Niks, E. H.; de Groot, I.; Katsalouli, M.; van den Anker, J.; Ward, L. M.; Leinonen, M.; D'Alessandro, A. DRAFT Efficacy and Safety of Vamorolone over 48 Weeks in a Randomized, Double-Blind Trial in Duchenne Muscular Dystrophy. Neurology **2023**, Draft.

(3) EXTERNAL COMPARISON OF RESULTS OF VAMOROLONE STUDY VBP15-004 WITH RESULTS OF THE FOR-DMD STUDY Company: Santhera (Switzerland) Pharmaceuticals, Ltd Release Date of Report: 23 Sep 2022; Santhera Pharmaceuticals, Ltd: Switzerland, 2022.

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(5) National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (accessed 2023-07-31).

(6) Noble-Longster, J.; Tolley, K.; Stainer, L.; Choong Wong, S.; Hariri, C.; Reuben, E.; Godfrey, J. Burden and Effects of Steroid Use in the Treatment of Duchenne Muscular Dystrophy., 2022.

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