Givinostat for treating Duchenne muscular dystrophy in people 6 years and over – ACM2

For public and projector – confidential information redacted

Technology appraisal HST committee 23rd October 2025

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Company: ITF Pharma

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

- ✓ **Recap from ACM1**
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Key issues link

Background on Duchenne muscular dystrophy

Fatal rare genetic disorder which begins in childhood and causes systemic loss of muscle function and progressive disability

Causes

- Rare progressive genetic condition caused by X-chromosome mutations in dystrophin gene (muscle function)

Epidemiology

- Approx. 100 boys born each year with DMD and 1,182 people are living with DMD in the UK.
- Mutation is on the X chromosome, almost exclusive prevalence of DMD in males. Age of onset usually 3-5 yrs.

Symptoms and prognosis

- DMD affects entire body, as it advances people lose ability to walk, use upper limbs, have weakening of breathing muscles, swallowing, bowel and digestion issues, skin effects and neurobehavioural comorbidities such as intellectual disability, attention deficit disorders and autism spectrum disorder.[1]
- Respiratory and cardiac function weaken progressively, leads to 24-hr assisted ventilation and cardiac failure.
- DMD requires increasing care as condition progresses culminating in 24-hr care with multiple carers
- DMD has profound and wide-ranging impact on patients and their families: physical, psychological and financial.
- Life expectancy of people with this fatal disease depends how quickly and intensely muscle weakness progresses: average lifespan less than 30 years due to respiratory and/or cardiac failure.

NICE

Abbreviations: DMD, Duchenne muscular dystrophy; UK, United Kingdom

1. Vaillend C, Aoki Y, et al Duchenne muscular dystrophy: recent insights in brain related comorbidities. Nat Commun. 2025 Feb

Key issues link

ACM1 summary: Call for additional evidence

Committee needs more information and analyses to determine cost-effectiveness

Issue	Detail	New evidence	Company BC	EAG BC
Treatment effect	Alternatives to using AFs	Yes	No changes	Updated
	Treatment effect beyond loss of ambulation	Scenarios	No changes	No changes
	Application of treatment effect in model	No	No changes	Updated
Resource cost	Further explore tertiary-care & medical-aid costs and scenarios differentiating HS 7/8	Scenario	No changes	Updated
Patient HRQoL	Utility source	No	No changes	No changes
	Increasing impact & differentiate HS 7/8	No	No changes	No changes
Carer HRQoL	Approach to modelling	No	No changes	Updated
	Utility source & differentiate HS 7/8	Yes – new data	Updated	Updated
	Number of carers	Yes – new data	Updated	No changes
	Life extension on carer HRQoL	Scenario	No changes	No changes

Abbreviations: AF, acceleration factor; BC, base-case; HRQoL, Health Related Quality of Life; HS, health state.

Key issues

Key issues link - summary

Issue	Modelling and assumptions around & link	Effect
1. Population	Evidence and modelled population is not full MA population	Unknown
2. Givinostat treatment effect	Estimation, post-LOA effect and application in model	Large
3. Non-reference discount rate	Which discounting rate to use	Large
4. Patient HRQoL	Patient utility source & differentiate HS 7 and 8	Large
5. Carer HRQoL	Carer utility source & differentiate HS 7 and 8	Large
6. Carer HRQoL	Number of carers	Large
7. Carer HRQoL	Approach to modelling	Large
8. Carer HRQoL	Life extension on carer HRQoL	Large
9. Resource cost	Tertiary-care and medical-aid costs & differentiate HS 7/8	Moderate

Resolved issue	Committee's preferred conclusions/assumptions
Comparators	ECM comparator based on treatment regimens used in EPIDYS
ECM data for MAIC	UK real-world dataset
Givinostat data for MAIC	Full givinostat population from EPIDYS and OLE study (n=224)
HERCULES NHM survival	Company's updated NHM suitable for decision- making

NICE **Abbreviations**: HRQoL, health Related Quality of Life; HS, health state.

Glossary of terms and abbreviations

Key issues link

Term	Definition	Abbreviation
Health state	Discrete health state in the model (8* in total and death)	HS
Loss of ambulation	Trial outcome (milestone) corresponding to ambulatory HS (early ambulatory to transfer). Informs transitions from ambulatory HS.	LOA
Non invasive ventilation	Trial outcome (milestone) broadly corresponding to HS with night ventilation. Informs non-ambulatory transitions.	NIV
Forced Vital Capacity <1litre	Trial outcome (milestone) broadly corresponding to HS with full ventilation. Informs non-ambulatory transitions.	FVC<1L
Acceleration factor	Ratio of median time to one outcome compared to another (e.g NIV / LOA).	AF
Continued Treatment effect	The effect of a treatment that persists because the treatment is still being administered	Continued TxE
Carryover treatment effect	Any residual effect of a treatment that remains after the treatment has been stopped and influences outcomes in subsequent periods	Carryover TxE
SOLVER	Excel function used to modify model transition HRs to match modelled medians to clinical medians.	SOLVER

Abbreviations: AF, acceleration factor; ECM, established clinical management; FVC<1L, forced vital capacity<1litre; GIV, givinostat; LOA, loss of ambulation; NIV, non-invasive ventilation; TxT treatment effect.
Notes: *8 health states are operationalised as 10 in the model due to differing routes of progression

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Key issues link

Patient perspectives 1/2

Two new patient statements received during CfE

In addition to points below, specific comments are presented alongside key issues.

- *Watching your child lose physical function and face early death while peers thrive is psychologically shattering.*
- *Progressive disability in DMD leads to total dependence, complex care needs, and irreversible decline.*
- *The mental health impact on both child and carer includes anxiety, depression, trauma, and chronic grief.*
- *Medical care for severely disabled children is riskier, more complex, and significantly more expensive.*
- *Families face extreme financial and emotional burdens due to systemic gaps in health and social care.*

- *DMD shapes your personality and experiences throughout your life.*
- *You lose ability after ability every year, it is depressing, constant and relentless.*
- *Providing support is so expensive, especially in later years.*
- *When DMD is all you know, you try to live the best life you can, which makes life worth living.*
- *Everyone with DMD would tangibly benefit from delayed progression.*

Abbreviations: CfE, Call for Evidence; DMD, Duchenne muscular dystrophy.

Key issues link

Patient perspectives 2/2

Responses from Action Duchenne, Duchenne UK, Muscular Dystrophy UK

In addition to points below, specific comments are presented alongside key issues.

- New unpublished Sheffield data on carer HRQoL and transcription of listening exercise with DMD patients, parents, and clinicians shared by Duchenne UK (discussed on slides about modelling carer HRQoL).
- Highlighted evidence limitations in rare diseases such as DMD and the need for qualitative evidence and pragmatic approach to uncertainty around key issues.
- Reinforced that individuals with DMD can lead purposeful and engaged lives across all stages of the condition. They pursue education, maintain friendships, engage in hobbies, and express aspirations for the future.
- Initial committee meeting and EAG assessment did not sufficiently reflect the complexity of later stages, nor the cumulative burden on families and carers.
- Explained the multifaceted, complex and cumulative nature of caring for someone with DMD. For example, note that death doesn't always occur in final stages. It can happen suddenly, and sometimes avoidably, at any point in the disease trajectory. Assumption, that death is a distant endpoint, fails to reflect lived reality of families affected by Duchenne.
- Slowing down muscle decline significantly impacts functional ability and independence at all stages of the condition, including end-stage.

Abbreviations: DMD, Duchenne muscular dystrophy; UK, United Kingdom; HRQoL, Health Related Quality of Life; EAG, external assessment group.

Key issues link

Clinical perspectives

Submissions from ABN, BPNA, and 2 clinical experts

In addition to points below, specific comments are presented alongside key issues

- Wanted to highlight devastating and life changing impact of DMD diagnosis on individuals, their carers and wider families. Support is needed for individuals with DMD as well as their carers and wider families.
- DMD is not simply muscle disease. Cardiac, respiratory, bone, gastrointestinal and renal impairments increase as disease progresses. Whilst we cannot yet cure DMD, at least we can delay it.
- Slowing down muscle decline has significant impacts not only on physical well-being but also on psychological health of individuals with DMD, their carers and wider families.
- Delaying progression, enable boys and young people with DMD to achieve goals and dreams and potentially have a better quality of life with purpose and meaning. For example, patients who lose ambulation later, appear to cope better. Without the delay, they would have to cope with school and bullying, transition to secondary school, time of hormonal change and loss of ambulation, all while wanting to be like everyone else.
- Shared some interim results from DMD QoL patients and carers survey (discussed on slides about modelling patient HRQoL)

Abbreviations: ABN, Association of British Neurologists; BPNA, British Paediatric Neurology Association – Muscle Interest group; DMD, Duchenne muscular dystrophy; DMD QoL Duchenne muscular dystrophy Quality of Life; HRQoL, Health Related Quality of Life.

Key issues link

Equality considerations 1/2

Duchenne UK and other stakeholders raised number of potential issues during CfE

Issue highlighted by stakeholders
Rare Diseases Disproportionately Affect Disabled and Paediatric Populations
NICE's Methods Guide Fails to Operationalise Flexibility
HRQoL and Carer Impact Data: A Systemic Gap
Restoring to full health need for 1.5% rate for cost and health effects. This can breach NICE's duty to consider equity and long-term societal impact.
Exclusion from Medicines for Children Policy
Paediatric HRQoL: issues measure including need for proxy data as well as lack of guidance in NICE manual
Exclusion of Non-Ambulant Children.
Exclusion of Social Care Costs
Lack of Trauma-Informed Practice
Inappropriate Standards for Paediatric Disability
Health Inequalities and Associative Discrimination in Employment of Duchenne Parent Carers
Intersectionality and Compounded Disadvantage of protected characteristics, including age, disability, sex, and pregnancy or maternity.

NICE

Abbreviations: CfE, Call for Evidence; DMD, Duchenne muscular dystrophy; HRQoL, health related quality of life; UK, United Kingdom. **Links:** NICE manual

Key issues link

Equality considerations 2/2

Duchenne UK and other stakeholders raised number of potential issues during CfE

Issue highlighted by stakeholders
NICE processes do not account for living with a severe disability or for those who will become wheelchair users.
Health inequalities – Disabled people have worse health outcomes
Parent carers (majority female) suffer poor health outcomes – gender also affected.

NICE

- NICE Manual includes flexibility to consider appropriately evidence in rare and paediatric diseases, carer HRQoL, paediatric HRQoL.
- Medicines for children policy is outside the scope of this appraisal.
- Non-ambulant population is discussed in Key issue 1 - Population.
- 1.5% discounting is discussed in Key issue 3 - Non-reference discount rate.
- Patient HRQoL is discussed in Key issue 4 - Patient HRQoL.
- Carer HRQoL is discussed in Key issues 5 to 8 - Carer HRQoL.
- Social care cost is discussed in Key issue 9 - Resource cost.
- Committee will consider whether the health inequalities relating to disability are captured in the model, and whether health inequalities experienced by carers are a relevant consideration.

Abbreviations: CfE, Call for Evidence; DMD, Duchenne muscular dystrophy; HRQoL, health related quality of life; UK, United Kingdom.

Links: NICE manual

For issues discussed at ACM1 please follow this link: ACM1- Equality consideration

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Key issues link

Key issue: Population

Scope defines population as people with DMD 6 years of age and older

Background

- Givinostat MA is for the treatment of DMD in patients aged 6 years and older.
- But company submission focuses on subgroup of DMD patients who are ambulant when they initiate givinostat (no stopping rule) based on available clinical data from EPIDYS and OLE.
- Conditional MHRA MA includes non-ambulatory patients (awaiting ULYSSES results due in 2028).

Stakeholders

- No evidence in non-ambulant population (people who start givinostat after LOA), but EMA granted licence including that population – indicates mechanism of action is potentially beneficial.
- Acknowledge that NICE can only make recommendation where evidence is available.
- Givinostat is not limited to muscles used for walking. It is biologically plausible that earlier treatment may have residual effects on muscle pathology beyond this point.
- Believe, all patients should have access to givinostat regardless of ambulation status. Ambulation is an arbitrary cut-off point that doesn't reflect the continued progression of the condition and the impact of delayed progression at any age.
- Suggest that excluding non-ambulant population is an equality issue.

Is the committee able to make recommendations for people who are non-ambulant at start of treatment?

- Recommendation for routine use and/or managed access?
- What is the committee's view on the equality issues raised?

NICE

Abbreviations: DMD, Duchenne muscular dystrophy; MA, Marketing Authorisation; MHRA; Medicines and Healthcare products Regulatory Agency; OLE, , Open Label Extension study. Equality issue slide summarises issues raised by stakeholders.

Key issues link

Recap: Givinostat treatment effect and its application

MAICs suggest GIV delays age at LOA, NIV & FVC<1L compared with ECM

		Observed GIV outcomes		Estimated GIV outcomes (AF*LOA)			
		Age at LOA		Age at NIV		Age at FVC <1L	
Data	N/ESS	Median (95%CI)	HR (95%CI) Robust SE	Median (95%CI)	HR (95%CI) Robust SE	Median (95%CI)	HR (95%CI) Robust SE
All GIV unadjusted	224.0	17.25	0.241 (0.176, 0.330)	25.92	0.247 (0.180, 0.338)	33.50	0.246 (0.173, 0.352)
ALL GIV weighted	151.9	17.97	**0.201 (0.142, 0.285)**	27.00	**0.206 (0.145, 0.293)**	34.90	**0.218 (0.149, 0.321)**
ECM UK RWD	156.0	12.28	-	18.46	-	23.86	-

Committee conclusion at ACM1

- Use the UK real-world dataset as a source for ECM data in the unanchored MAIC.
- Use the full givinostat population from EPIDYS and the OLE study (n=224) in the unanchored MAIC.

Abbreviations: MAIC, matching-adjusted indirect comparison; EAG, external assessment group; ECM, established clinical management; ESS, effective sample size; GIV, givinostat; FVC<1L, forced vital capacity<1litre; HR, hazard ratio; LOA, loss of ambulation; SE, standard error.

Key issues link

Introduction to treatment effect

Background

- The treatment effect of givinostat is how much it delays progression through various health states.
- MAIC shows clinical treatment effect on 3 trial milestones: LOA, and NIV and FVC<1L (via acceleration factors).
- In the model it is applied through 9 approximated hazard ratios for the model health state transitions.

Committee will be presented with

- Company base case: and scenarios exploring alternative modelling and additional treatment effect.
- EAG base case: and scenarios exploring modelling of additional treatment effect.

Committee will be asked to decide

1. Whether or not the company base case models a treatment effect beyond loss of ambulation?
2. Should givinostat treatment effect be modelled beyond loss of ambulation?

Upcoming slides

1. Explanation of modelling in the ECM arm – Slide 17
2. Explanation of company modelling of relative effectiveness of givinostat – Slides 18-19
3. Summary of the company and EAG responses to the call for evidence – Slide 20
4. Comparison of treatment effect implied by company and EAG base cases on the three milestones - Slides 21-22
5. Comparison of treatment effect implied by scenarios on the three milestones – Slides 23-24
6. Interpretation of treatment effect – Slide 25
7. Stakeholder responses and key question reminder – Slide 26

Abbreviations: AF, acceleration factor; CINRG, Cooperative International Neuromuscular Research Group; EAG, external assessment group; ECM, established clinical management; GIV, givinostat; KM, Kaplan-Meier; LOA, loss of ambulation; NIV, non-invasive ventilation; UK RWD, United Kingdom real world data.

Recap: The NHM, ECM data and age at LOA

Key issues link
Intro to treatment effect

No KM curves available for LOA data in UK RWD, only median reported

Company – NHM to model ECM:

- Natural history model (NHM) constructed using transition probabilities from D-RSC data and two other sources.
- Original NHM overpredicted survival compared to expert opinion and LOA compared to UK RWD.
- "Analysis 2" used SOLVER to vary HRs for the first 3 transitions in the model, and for mortality transitions from health state 8a and 8b to better align with UK RWD LOA and expert survival estimates at 50 years.
- This makes up basis of the ECM arm and both base cases.

Median	Original NHM	UK RWD	Analysis 2
Loss of ambulation	15.5	12.2	12.1
Starting Ventilation	19.6	18.1	16.0
Full time ventilation	23.9	20.5	20.3

EAG:

- Using SOLVER does not preserve the underlying survival distribution.
- SOLVER matches median LOA but overestimates tail - leading to higher % of patients with later age at LOA than expected (in bold).
- This is a source of residual uncertainty and could explain the implausible results when applying MAIC HRs directly to NHM.

% LOA	SOLVER – adjustment (yrs)	UK registry study (yrs)
25%	9.8	10.2
50%	12.1	12.2
75%	**15.3**	**13.7**

Abbreviations: AF, acceleration factor; CINRG, Cooperative International Neuromuscular Research Group; EAG, external assessment group; ECM, established clinical management; GIV, givinostat; KM, Kaplan-Meier; LOA, loss of ambulation; NIV, non-invasive ventilation; UK RWD, United Kingdom real world data: D-RSC, Duchenne Regulatory Science Consortium.

Recap: Company approach: extrapolating GIV data

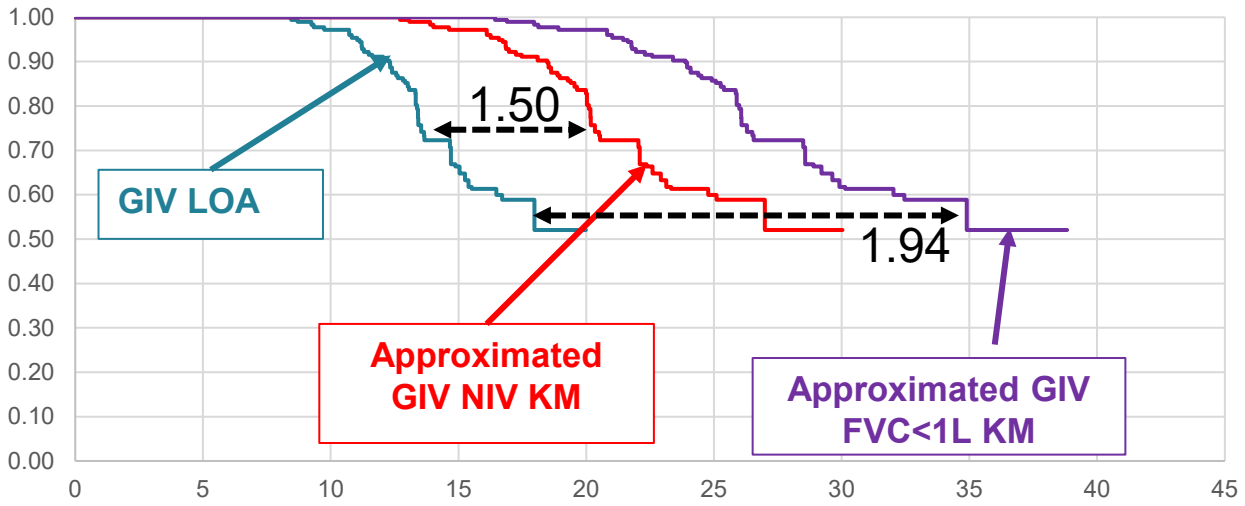
Problem: There were no events for NIV or FVC<1L in the EPIDYS/OLE trial

UK-RWD study (ECM)

Outcome	Median age, years	AF
LOA	12.28	-
NIV	18.46	1.50 (18.46/12.28)
FVC<1L	23.86	1.94 (23.86/12.28)

Company approach:

1. **Calculate AFs from UK RWD medians**:
- *"NIV happens on average 1.5 times later than LOA"*
- *"FVC<1L happens on average 1.94 times later than LOA"*



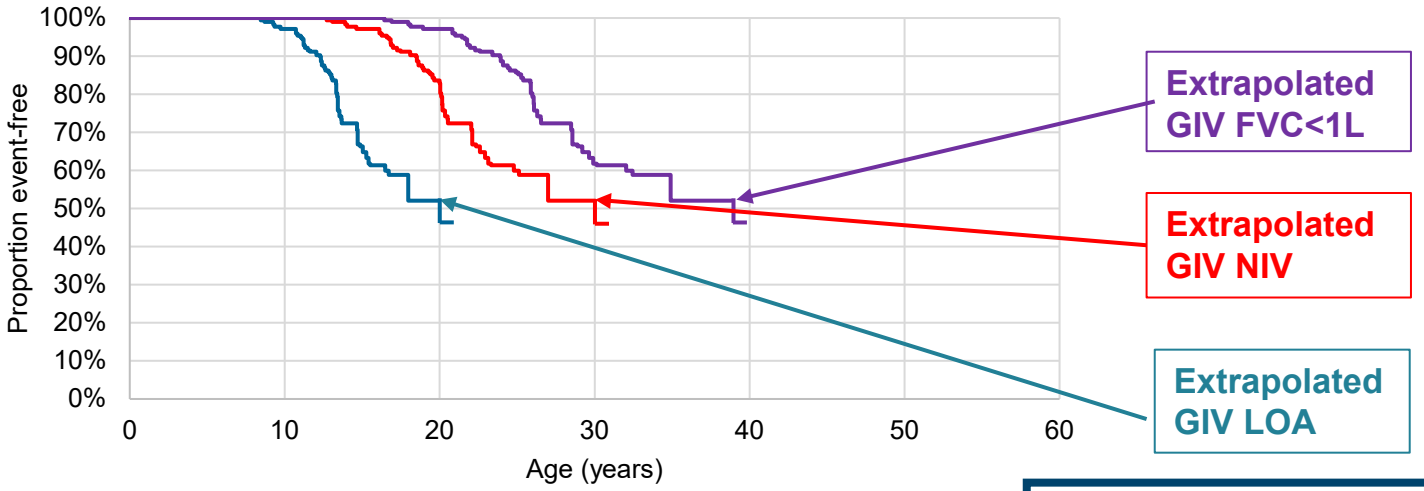
2. Apply those acceleration factors to the MAIC adjusted givinostat LOA KM curve to approximate givinostat NIV and FVC<1L KM:
- AF1.50 * GIV LOA KM= GIV NIV KM
- AF1.94 * GIV LOA KM = GIV FVC<1L KM

NB: No LOA KM data available for ECM from UK RWD. So, LOA/NIV acceleration factor also used to approximate this data for use in the MAIC.

Abbreviations: AF, acceleration factor; EAG, external assessment group; ECM, established clinical management; FVC<1L, forced vital capacity<1litre; GIV, givinostat; LOA, loss of ambulation; MAIC, matching-adjusted indirect comparison; NIV, non-invasive ventilation; OLE, open label extension study; UK RWD, United Kingdom real world data.
Please note: Diagram is illustrative only, does not show either base case

Recap: Company approach: SOLVER and modelling GIV

Problem: There are 3 disease milestones but there are 8 health states in model



3. Median values for NIV and FVC<1L obtained from MAIC adjusted KM:
- Goal values for SOLVER

SOLVER	LOA	NIV	FVC<1L
Goal	17.97	27.00	34.90
Modelled	18.17	27.00	34.83
SOLVER HR	0.50	0.40	0.46
Difference	0.20	0.00	0.07

4. Use the SOLVER function in Excel to modify the HRs for each transition probability until the modelled medians for each milestone match the extrapolated medians:
- SOLVER HRs are applied to model transitions

	Company
HS1 to HS2	0.50
HS2 to HS3	0.50
HS3 to HS4	0.50
HS4 to HS5	0.40
HS5 to HS7a	0.40
HS7a to HS8a	0.46
HS4 to HS6	0.40
HS6 to HS7b	0.46
HS7b to HS8b	0.46

Abbreviations: AF, acceleration factor; EAG, external assessment group; ECM, established clinical management; FVC<1L, forced vital capacity<1litre; GIV, givinostat; HR, hazard ratio, HS, health state; LOA, loss of ambulation; NIV, non-invasive ventilation.
Please note: Diagram is illustrative only, does not show either base case

Key issues link
Intro to treatment effect

GIV treatment effect: CfE response summary

There is large uncertainty around modelling of GIV treatment effect (TxE)

CfE request	Company	EAG
1. Explore alternatives to AFs	• Retains AF*LOA based approach • Provides evidence supporting AF.	• Prefer new approach (DIFF) applying treatment effect to time between milestones to model NIV & FVC. • Consider evidence supporting AF is flawed.
2. Clarify whether AFs models TxE beyond LOA	• Maintain that AF approach does not model direct TxE beyond LOA (which is conservative).	• Further explain that AF mathematically models a post-LOA treatment effect. • AFs are not conservative, they assume constant TxE beyond LOA (even in presence of discontinuation).
3. Justify magnitude of TxE beyond LOA	• TxE beyond LOA is not modelled but clinically plausible. • Scenarios explore post LOA TxE on NIV and FVC (20% improvement in SOLVER HRs & alternative AFs).	• Agree TxE beyond LOA is plausible, but continued TxE is modelled by company over full time horizon. • Company model ongoing benefit despite reasonably high discontinuation and reduction in costs. • Scenarios explore 50% and 100% of LOA TxE applied to NIV to explore post LOA TxE.
4. Present updated modelling	• No changes to modelling approach • Retains use of AFs and SOLVER. • Applying HRs directly to HSs results in clinically implausible results.	• Maintain applying HRs directly is technically appropriate but acknowledges implausible results. • Use SOLVER as less biased than direct HR. • Use new DIFF approach instead of AFs.

Abbreviations: AF, acceleration factor; CfE, Call for Evidence; FVC, forced vital capacity<1litre; GIV, givinostat; LOA, loss of ambulation; NIV, non-invasive ventilation; TxE, treatment effect; DIFF, EAG's treatment affect applied to difference approach.

Treatment effect estimation: estimating NIV & FVC

Key issues link
Intro to TxE

Problem: Company and EAG disagrees if using AFs assumes TxE beyond LOA

EAG on company approach (AF):

- Applies AF - milestones ratio from ECM to whole age at LOA milestone.
- Models a constant treatment effect across whole time horizon. As shown by 46% improvement in all endpoints.

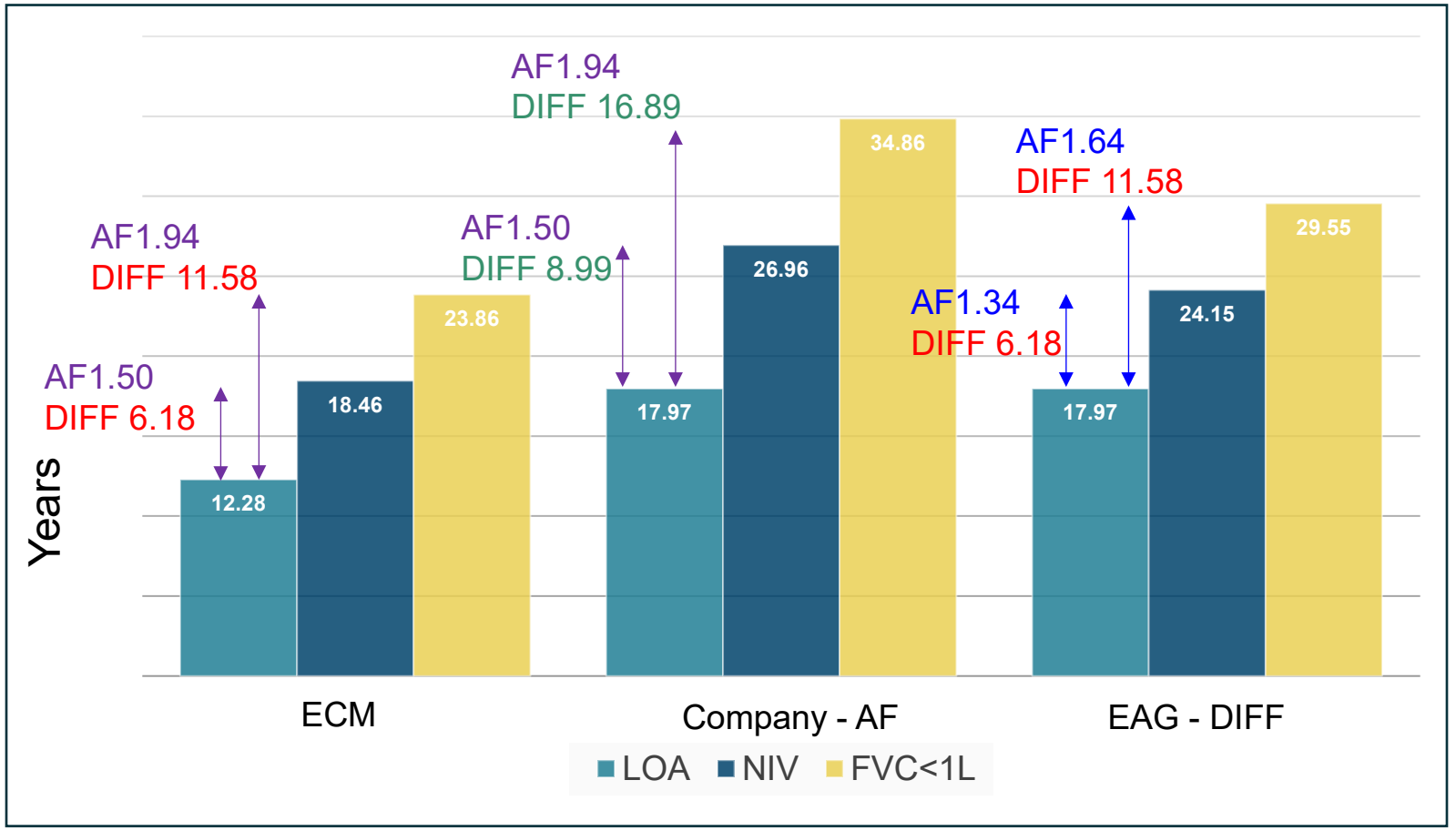
EAG on EAG approach (DIFF):

- If no treatment effect beyond LOA is assumed, the implied treatment effect acceleration factor should decline.
- EAG prefers to apply any treatment effect to the time between milestones, rather than the milestones themselves.
- This approach delays givinostat medians by the time LOA was delayed and does not assume effect beyond LOA:
  - GIV effectiveness decreases over time: NIV and FVC<1L are delayed by 31 & 24% respectively.
  - Implied GIV milestones AFs are lower too, 1.34 & 1.66 for NIV & FVC respectively (vs 1.50 & 1.94).

		Company approach: **AF**			EAG approach: **DIFF**	
	ECM (years)	**AF (ECM ratio)**	**Median (years) calculated as AF*LOA**	**AF TxE (ratio)**	**Delay in LOA (yrs)**	**Median (yrs) calculation (delay)**	**DIFF TxE (ratio)**
LOA	12.28	-	17.97	**1.46**	-	17.97	**1.46**
NIV	18.46	1.50	26.96 (LOA x 1.50)	**1.46**	6.18	24.15 (LOA+6.18)	**1.31**
FVC	23.86	1.94	34.86 (LOA x 1.94)	**1.46**	5.4	29.55 (NIV+5.4)	**1.24**

Abbreviations: AF, acceleration factor; EAG, external assessment group; DIFF, difference; FVC<1L, forced vital capacity<1litre; GIV, givinostat; LOA, loss of ambulation; NIV, non-invasive ventilation; TxE, treatment effect.
Note: all values in table are calculated using clinical medians before SOLVER adjustments.

Visual representation of company and EAG base cases



Different approaches result in the SOLVER function estimating different HRs for each transition:

	Company	EAG
HS1 to HS2	0.50	0.51
HS2 to HS3	0.50	0.51
HS3 to HS4	0.50	0.51
HS4 to HS5	0.40	0.62
HS5 to HS7a	0.40	0.62
HS7a to HS8a	0.46	0.77
HS4 to HS6	0.40	0.62
HS6 to HS7b	0.46	0.77
HS7b to HS8b	0.46	0.77

Does the company's approach model a treatment effect beyond LOA?

Abbreviations: AF, acceleration factor; EAG, external assessment group; DIFF, difference; FVC<1L, forced vital capacity<1litre; GIV, givinostat; LOA, loss of ambulation; NIV, non-invasive ventilation; HR, hazard ratio; HS, health state.

Exploring treatment effects beyond LOA: Company modelling

	Company					
	Base case		A) 20% improvement in NIV & FVC		B) alternative AFs 1.98 & 2.26	
	GIV	AF TxE	GIV	AF TxE	GIV	AF TxE
LOA	**17.97**	**1.46**	17.97	1.46	17.97	1.46
NIV	**26.96**	**1.46**	28.58*	1.55	35.58	1.93
FVC <1L	**34.86**	**1.46**	37.75*	1.58	40.61	1.70

Company:

- Base case does not model any specific givinostat effect beyond LOA (aside from simply delaying subsequent milestones by the delay in LOA) thus it is conservative.
- Expect givinostat to have an effect beyond LOA and presents extra scenarios a) assuming 20% improvement (vs ECM HRs) in non-ambulatory HS, and b) using AF from Bach and Martinez.

EAG:

- Agree givinostat effect post LOA is plausible albeit uncertain, but the company base case already models such an effect. Therefore, the company's scenarios are double counting as shown by increasing TxE.
- Any scenario that does not model a constant treatment effect over the time horizon of the model for each milestone implies a reduction in AF for later milestones (age at NIV and age at FVC <1L).
- Additional uncertainty as median age when GIV is stopped is earlier than median age at NIV in both approaches. This more or less aligns with HS 4 in both company and EAG's approaches.

Abbreviations: AF, acceleration factor; EAG, external assessment group; FVC<1L, forced vital capacity<1litre; HS, health state; LOA, loss of ambulation; NIV, non-invasive ventilation.

Note: all values in table calculated using clinical medians before SOLVER except for scenario A where there are no clinical medians*.

Exploring treatment effects beyond LOA: EAG modelling

	EAG					
	Base case		C) 50% LOA effect added to NIV transitions		D) 100% LOA effect added to NIV transitions	
	GIV	DIFF TxE	GIV	DIFF TxE	GIV	DIFF TxE
LOA	**17.97**	**1.46**	17.97	1.46	17.97	1.46
NIV	**24.15**	**1.31**	25.55	1.38	26.99	1.46
FVC <1L	**29.55**	**1.24**	30.95	1.30	32.39	1.36

EAG:

- Acknowledge there may be some treatment effect beyond LOA and even beyond discontinuation, but assuming constant effect, regardless of discontinuation, as per company base case is clinically implausible.
- This remains a significant uncertainty that the additional evidence provided by company doesn't address.
- Offers Scenarios which extend treatment effect (50% and 100% of LOA AF) to NIV, but not FVC<1L.
- EAG clinical advice noted ongoing effect on FVC was less certain due to accumulating fibrosis.
- Alternatively, a more useful model structure would explore treatment effect only on treatment (this would not be compatible with SOLVER).

Abbreviations: AF, acceleration factor; EAG, external assessment group; FVC<1L, forced vital capacity<1litre; HR, hazard ratio; LOA, loss of ambulation; NIV, non-invasive ventilation.

Note: all values in table are calculated using medians before SOLVER adjustments

Interpreting modelling of treatment effect

Key issues link
Intro to treatment effect

Scenario	Effect type	Interpretation
EAG base case	"Delay only effect"	Givinostat affects time to loss of ambulation but no treatment effect on subsequent milestones beyond the delay from LOA (delays by same amount as LOA).
EAG scenario 2 (50% of TxE to NIV)	"Carryover effect"	Givinostat affects loss of ambulation and has a smaller effect on NIV* but does not affect FVC<1L.
EAG scenario 3 (100% of TxE to NIV)	"Carryover effect 2"	Givinostat affects time to LOA and NIV* to the same degree, but does not affect time to FVC<1L.
Company base case	"Direct treatment effect"	Givinostat has a constant treatment effect to all people across all milestones, regardless of discontinuation.
Company scenario 2 (20% increase to base case TxE)	"Increasing treatment effect"	Givinostat has a treatment effect on LOA and a greater treatment effect on NIV and FVC<1L.

* Effect on NIV (and on FVC<1L) is potentially due to ongoing treatment (direct effect) or potentially due to being in better health when ambulation is lost (carryover effect). The contribution of each component is unclear. Direct treatment effect would be expected to stop with treatment discontinuation but carryover effect would be expected to continue.

Abbreviations: EAG, external assessment group; FVC<1L, forced vital capacity<1litre; HR, hazard ratio; HS, health state; LOA, loss of ambulation; NIV, non-invasive ventilation; TxE, treatment effect.

Key issues link
Intro to treatment effect

Key Issue: Treatment effect

Clinical opinion: treatment beyond LOA is plausible

Stakeholders:

- No direct clinical evidence, although ongoing studies (e.g. ULYSSESS results due in 2028).
- Suggest to use expert opinion to inform these assumptions around treatment effect.
- All/most agree treatment beyond LOA is plausible.
- Note DMD is rare disease so uncertainty is expected.
- If treatment effect beyond LOA is not modelled directly, it still should be considered.
- Givinostat's mechanism of action is systemic and not limited to muscles used for walking.
- It is reasonable to infer a similar effect as seen in corticosteroid treatment in DMD.
- Delay in milestone will not only see a shift in the milestone but an exponential improvement and delay.
- Those receiving Givinostat in EPIDYS continued to worsen, just at a decreased rate.

"*. . . it is biologically plausible that earlier treatment may have residual effects on muscle pathology beyond this point [LOA]. Givinostat's mechanism of action is systemic and not limited to muscles used for walking.*"

Does the company's approach model a treatment effect beyond LOA?
How should any givinostat treatment effect be modelled beyond loss of ambulation?

Abbreviations: AF, acceleration factor; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; LOA, loss of ambulation; NIV, non-invasive ventilation

Key issues link

Key issue: Non-reference discounting

CfE: reference-case discount rate of 3.5% for costs and health effects should be applied

Company:

- changed use of 1.5% discount rate to health outcomes from year 30 onwards to the whole model horizon:
  - Because NICE criteria for non-reference discounting exclude DMD and similar chronic paediatric conditions as they cannot be **restored to full or near-full health** (one of three NICE manual criteria), despite benefits accruing over a long time.
  - As givinostat meets the other two criteria (**technology is for people who would otherwise die or have a very severely impaired life,** and **benefits are likely to be sustained over a very long period**).

Stakeholders

- "Full health" need for 1.5% discounting can breach NICE's duty to consider equity / long-term societal impact.

EAG & NICE:

- EAG reiterates that there is no long-term evidence of benefit for givinostat and no evidence of restoring to full or near-full health.
- EAG notes that the 1.5% rate is also used for QALY shortfall calculation which is not appropriate.
- Clinicians noted that cure could be developed in future, but noted challenges, including for gene therapy
- NICE technical team notes that there is no provision for changing discount for health-outcomes only.

What discounting is appropriate for decision making?

NICE

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, external assessment group; QALY, quality adjusted life year .

Links: NICE manual. Equality issue slide summarises issues raised by stakeholders.

Key issues link

Patient Health-related quality of life: source

	Company: Audhya 2023	EAG: BOI study	Scenario: Landfeldt 2017	Scenario: Crossnohere 2021
Tool	EQ-5D-5L	DMD-QoL	HUI	EQ-5D-3L
N	N=63	N=24	N=770 (191 UK patients)	N=263 (74 UK participants)
% self-report	Patients (12-40 years) – 76% self-reports*	Patients (DMD ≥ 24 months) – 100% self reports	Patients (5+ years) – all carers reports – 0% self-reports	Adult patients (n=61), carers of minors (n=134) & adults (n=68) – 23% self reports
HS	4: with 13 substates	8	4 or 5	4
Responses per HS	8 to 23: substates 1 to 16	0 to 8: Landfeldt used for HS1	154 to 256**	31 to 111
Location	US	UK	Germany, Italy, UK, US	Australia, Belgium, Netherlands, CAN, UK, US
Value set	US value set	UK value set	Canadian value set	US tariff
HS 7/8	0.14	0.52 vs 0.33	0.15 or 0.13 vs 0.05**	0.26

Note: as discussed at ACM1 using BOI changes severity modifier from 1.7 to 1.2 – see Severity modifier slide

Abbreviation: BOI, Burden of Illness study; DMD, Duchenne Muscular Dystrophy; EAG, external assessment group; EQ-5D-5L, European Quality of Life 5 dimensions 5 level version; HIU, Health Utilities Index Questionnaire; QoL, Quality of life.

Notes: *, of these 47% needed only transcribing responses; ** , using generalised linear regression model 2 (GLM2) or combining GLM2 and ventilatory GLM3.

Patient health-related quality of life: comments

Key issues link

Company:

- Did not map PedsQL data from EPIDYS OLE to EQ-5D to avoid introducing uncertainty. Data has high missingness (due to COVID) and the mapping algorithms are unsuitable for boys with DMD.
- Also there are limited or no observations from the OLE study for later health states.
- PODCI data only collected at baseline and weeks 48 and 72 of EPIDYS, not a robust foundation for CEM.

EAG:

- Would prefer company to at least explore utility data from EPIDYS by mapping PedsQL or PODCI to EQ-5D.
- NICE methods suggest using observational utility data if no data available from clinical trials.

Stakeholders

- Noted unsuitability of EQ5D data and suggested to combine qualitative insights with expert opinion and available data to reflect the real-world impact of disease progression.
- All agreed there is a large difference between state 7 and 8, most advanced stages of DMD.
- But highlighted importance of early non ambulatory states, and specifically preserving HTMF.
- Explained that maintaining trunk and upper limb function is critical for independence, dignity and confidence
- Concerns BOI values do not reflect disease progression.
- Patient expert (testimony at ACM1) felt that BOI values did not have face validity.

"I was diagnosed with DMD when I was three years old, so living with this condition is all I have ever known. So it is quite difficult to have an objective view. "... So maybe I underestimate how bad things are."

NICE

Abbreviations: DMD, Duchenne muscular dystrophy; HS, health state; EAG, external assessment group; QoL, Quality of life; HTMF, hand-to-mouth function.

Key issues link

Key issue: Patient health-related quality of life

Company and EAG disagree on patient utility set (alternative scenarios available)

Utilities	Company: Audhya 2023	EAG: BOI
1. Early ambulatory	0.79	0.70*
2. Late ambulatory	0.64	0.49
3. Transfer	0.64	0.38
4. HTMF, no ventilation	0.28	0.54
5. No HTMF, no ventilation	0.25	0.51
6. HTMF, night-time ventilation	0.26	0.53
7. No HTMF, night-time ventilation	0.14	0.52
8. Full-time ventilation	0.14 [0.055 with multiplier]	0.33 [0.13 with multiplier]

Company

- Audhya is preferred as mostly self-reports, EQ-5D-5L (which was then crosswalked to EQ-5D-3L) and as reporting 13 disease stages
- BOI, although also self-reports, has very small number of responses per HS (0 to 8): not reliable

EAG

- BOI only UK study, has patient reported utilities, aligns with HERCULES model and different HS7 and 8
- Differentiates between health state 7 and 8
- Limited as not on EQ-5D scale
- Audhya is US study with US value set: not relevant

Which patient utilities are preferred for decision making?

Abbreviations: BOI, Burden of Illness study; EAG, external assessment group; EQ-5D-5L, European Quality of Life 5 dimensions 5 level version; EQ-5D-3L, European Quality of Life 5 dimensions 3 level version; HS, health state; HTMF, hand-to-mouth function; UK, United Kingdom.

Note: *, value from Landfeldt 2017 as no response recorded for HS1. Equality issue slide summarises issues raised by stakeholders.

Carer utilities

Please note the following slides discuss issues which some people may find distressing

Key issues link

Introduction to modelling caregiver HRQoL

Background

- DMD has substantial and ongoing effect on carers, it is important to capture this appropriately in the model
- Carer HRQoL is modelled as per NICE methods but there is disagreement on how carer HRQoL should be modelled and a lack of consensus in the literature.

Committee will be presented with

- Four aspects of modelling carer HRQoL will be presented to committee with a conclusion required on each

Committee will be asked to decide

1. Which source to use to inform carer utilities?
2. How many carers should be modelled in each health state?
3. Which approach should be used to implement the carer utilities in the model?
4. If and how to apply additional modelling around an extension to life benefit?

Upcoming slides

1. Information on the source and scenarios for carer utility data – Slides 33-34
2. Information on the number of carers for different health states in DMD – Slides 35-36
3. Information on the approaches which can be used to model carer HRQoL – Slides 37-41
4. Discussion on modelling of an extension to life benefit for different approaches in the base cases? Slides 41-43
5. Summary and key questions – Slide 44

NICE

Abbreviations: AF, acceleration factor; CINRG, Cooperative International Neuromuscular Research Group; EAG, external assessment group; ECM, established clinical management; GIV, givinostat; KM, Kaplan-Meier; LOA, loss of ambulation; NIV, non-invasive ventilation; UK RWD, United Kingdom real world data.

Key issues link
Intro carer HRQoL

Carer HRQoL: Sheffield data received during CfE

Both Company and EAG utilise new data, but have different approach

Sheffield data: UK EQ-5D-5L (which was then crosswalked to EQ-5D-3L) using UK values.

Company Sheffield 1 [redacted]	Ambulatory (HS1-2)	Transfer (HS3)	Non-ambulatory (HS4-8)
Utility value	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]

Scenario Sheffield 2 [redacted]*	Ambulatory (HS1-2)	Transfer (HS3)	HS4	HS5	HS6	HS7	HS8	Proxy for HS 8 - full time ventilation + HTMF
Utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG Sheffield 3 [redacted]*	Ambulatory (HS1-2)	Transfer (HS3)	HS4	HS5 to HS 8 – weighted average by sample size as low number of responses per state
Utility value	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]

- Other scenarios are available. Key studies slide summarises Sheffield and Landfeldt studies characteristics.

Abbreviations: UK, United Kingdom; HRQoL, Health Related Quality of Life; HS, health state; CfE, call for evidence; EAG, external assessment group; EQ-5D-5L, European Quality of Life 5 dimensions 5 level version; EQ-5D-3L, European Quality of Life 5 dimensions 3 level version; HTMF, hand-to-mouth function **Notes:** *, [redacted] as extra [redacted] Full time ventilation + HTMF (proxy for HS8)

Key issues link
Intro carer HRQoL

Key Issue: Carer HRQoL - Source

Problem: low number of responses in non-ambulatory HS in Sheffield data

Company: does not differentiate between HS4 and 8
EAG: does not differentiate between HS5 and 8

Stakeholders comments

- Limited data on carers and impact of DMD on parents and families.
- Utilities do not measure carer's HRQoL well, not sensitive enough.
- Carer HRQoL should not be limited to the degree of physical care required to support individual with DMD.
- There is a large difference between state 7 and 8.
- But highlighted the effect of losing HTMF or introducing ventilation and full-time ventilation on carers.
- Milestones represents shifts in physical capability and independence, and therefore shift in care needs.
- Suggest combining caregiver testimony, and clinical expertise, to inform utility estimates.
- Committee should acknowledge rate of progression, which is not captured in static utilities (slower progression reduces emotional distress).

"As he lost upper body function, I did everything for him: brushing his hair, brushing his teeth, dressing, washing, facilitating, adjusting his glasses, scratching his nose, putting his headphones on, passing him whatever he needed. Feeding him when his arms were too difficult to move. Moving his body became like lifting a futon—heavy, awkward, no resistance."

What carer utility set is preferred for decision making?

Abbreviations: DMD, Duchenne muscular dystrophy; HRQoL, Health Related Quality of Life; HS, health state; EAG, external assessment group; HTMF, hand-to-mouth function. Equality issue slide summarises issues raised by stakeholders.

Carer HRQoL: Number of carers

Key issues link
Intro carer HRQoL

New data from unpublished Sheffield study used by company

CfE: asked for scenarios exploring between 1 and 2 carers in ambulatory HS, and 2 for non-ambulatory HS

[redacted]*	Ambulatory (HS1-2)	Transfer (HS3)	Non-ambulatory (HS4-8)	Non-ambulatory by HS [redacted]				
				HS4	HS5	HS6	HS7	HS8
Informal carers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paid carers	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]*

Company

- Based on Sheffield data increased number of carers to 2 (ambulatory) and 3 (non-ambulatory)

EAG

- Sheffield utility values derived from parents or people with parental responsibility. Generalisability to other informal carers unclear. Appropriate to align utility values with people they apply to.
- Acknowledges that DMD affects all carers. But the model accounts for average full time informal carers over time horizon
- Unclear whether the number of informal carers relates to full time carers
- Therefore, made no changes and model 1 carer for ambulatory states and 2 for non-ambulatory states in base case.

Model	Company	EAG
HS1 - 3	2	1
HS4 - 8	3	2

Abbreviations: HRQoL, Health Related Quality of Life; HS, health state; CfE, call for evidence; EAG, external assessment group; HTMF, hand-to-mouth function. **Notes:** *, includes proxy measure for HS 8 from [redacted] patients in Full time ventilation + HTMF as no values were recorded for HS8

Key Issue: Carer HRQoL - Number of carers

Key issues link
Intro carer HRQoL

Company's and EAG's differ in assumptions around number of cares needed

Stakeholders

- Multiple carers are involved at every disease stage.
- Carers need to manage and support others in the caregiving network and the intensity of coordination increases as the disease progresses.
- Some suggested 2 carers are impacted across all health states, reflecting the shared nature of caregiving in most families (model should assume two carers throughout disease course).
- Some supported company's updated approach based on the Sheffield data.

"Employing carers gives you choice and control, but comes with a lot of work and emotional baggage, constantly worrying whether you will find somebody willing to look after you or whether you will be abandoned."

"It's a full-time job just managing the care team. I'm constantly checking stock, ordering supplies, coordinating shifts. Even with paid carers, I'm always on call."

"The diagnosis shattered our world. I was thrust into a role I never asked for—carer, advocate, medical coordinator, and emotional anchor."

How many carers should be modelled in ambulatory and non-ambulatory health states?

Abbreviations: EAG, external assessment group; HRQoL, Health Related Quality of Life; HS, health state; HTMF, hand-to-mouth function. Equality issue slide summarises issues raised by stakeholders.

Carer HRQoL: Introducing approaches

Key issues link
Intro carer HRQoL

Carer QALY trap: an occurrence in HTA modelling where a treatment extending life might reduce total carer QALYs by extending time in health states which have a loss of QoL

Increments relative to midway (Company base case ACM1 & 2)

- In/decrements calculated by subtracting utility for given HS from midway HS value (HS 4 HTMF, no ventilation)
- In/decrements applied to incremental LY (models QoL for extended time in HSs), thus QALY's are only applied to treatment (comparator has zero carer QALYs)
- Mitigates carer QALY trap, increments in earlier health states provide QALYs for increased time in those states
- But QALY trap can occur as increased time in later states still applies decrements
- It is a relatively novel approach

Carer disutilities (EAG ACM1 base case)

- Applies a reduction in utility to carers based on the health state of their patients
- Decrement could be calculated from general population utility or from least severe HS (HS1 early ambulatory)
- Allows carer QALY trap because extending life also extends the disutilities applied
- It is a prevalent approach

Carer utilities (EAG ACM2 base case)

- Actively models carers in the model by applying HS utilities (absolute QALYs of each carer calculated)
- Avoids carer QALY trap as extending life in any health state also improves the carer QALYs to some extent
- Unlike the other 2 approaches, it does not need anchor to calculate in/decrements as utility is applied directly
- It is a common approach

Abbreviations: HRQoL, Health Related Quality of Life; HS, health state; EAG, external assessment group; QALY, quality adjusted life year; HTMF, hand-to-mouth function. **Note:** Only approaches modelled in a base case in this appraisal shown here.

Carer HRQoL: Approaches - applied to Sheffield 1 & 3

Key issues link
Intro HRQoL

Health states	Sheffield 1		Sheffield 3	
	Utility	Company: Increments to midway	EAG: Utility	Increments to midway
Anchor (calculation)	NA	[redacted] = HS4 (HS-HS4)	NA	[redacted] = HS4 (HS-HS4)
1 - Early ambulatory	[redacted]	[redacted]	[redacted]	[redacted]
2 - Late ambulatory	[redacted]	[redacted]	[redacted]	[redacted]
3 - Transfer	[redacted]	[redacted]	[redacted]	[redacted]
4 - HTMF, no ventilation	[redacted]	**0.000**	[redacted]	[redacted]
5 - No HTMF, no ventilation	[redacted]	0.000	[redacted]	[redacted]
6 - HTMF, night ventilation	[redacted]	0.000	[redacted]	[redacted]
7 - No HTMF, night ventilation	[redacted]	0.000	[redacted]	[redacted]
8 - Full time ventilation	[redacted]	0.000	[redacted]	[redacted]

Company: increments to midway approach:

- **Sheffield 1 -** result in positive (but decreasing) increments in 1/2 and 3 “rewarding” less severe states. No decrements are applied for HS4-8 because all use an average utility.
- **Sheffield 3 -** positive (decreasing) increments in 1/2 and 3, zero increment in HS4 & same decrements in HS5-8

EAG: utility approach

- **Sheffield 3 -** Utility values decrease from state 1/2 to 5 (with same values states for HS5-8).

Next slide: carer QALY gain with both approaches using company’s assumptions (also illustrating Sheffield 1).

NICE **Abbreviations:** HRQoL, Health Related Quality of Life; EAG, external assessment group; QALY, quality adjusted life year.

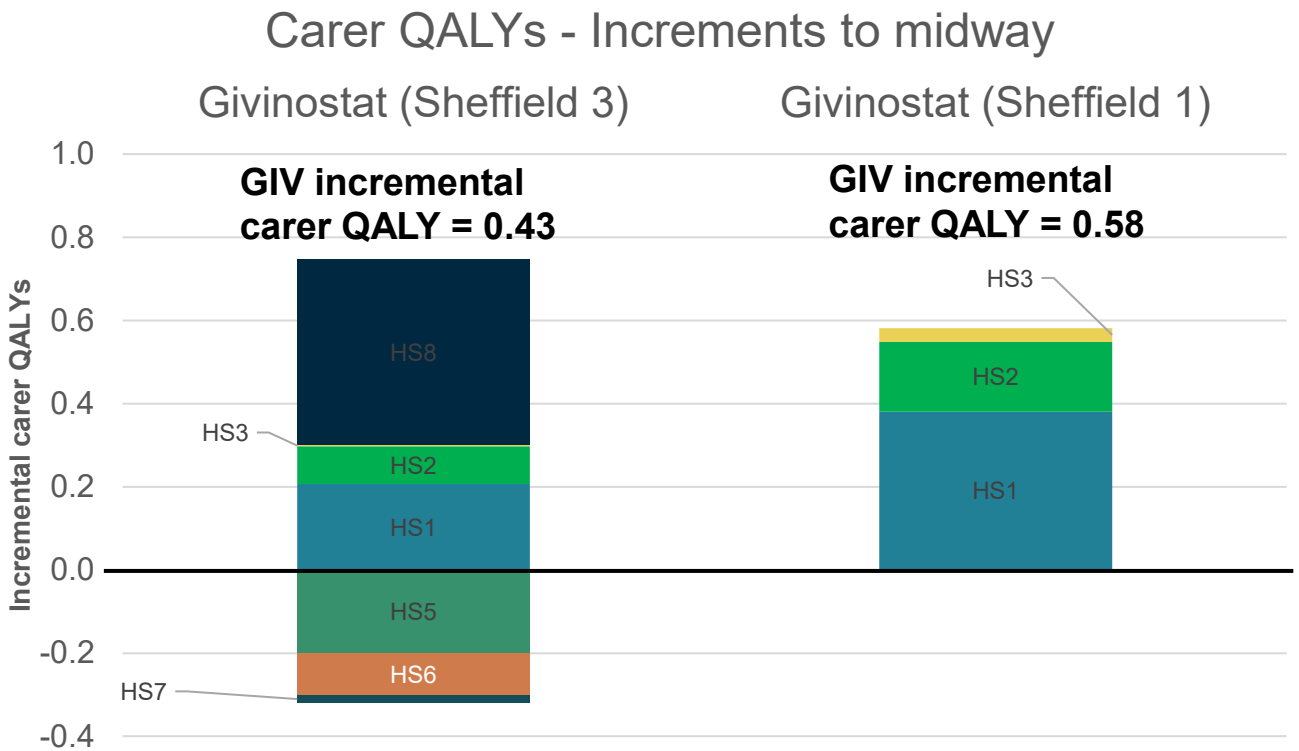
Note: Company’s model includes state 9 – death. Assumptions around state 9 are discussed later Life extension on carer HRQoL

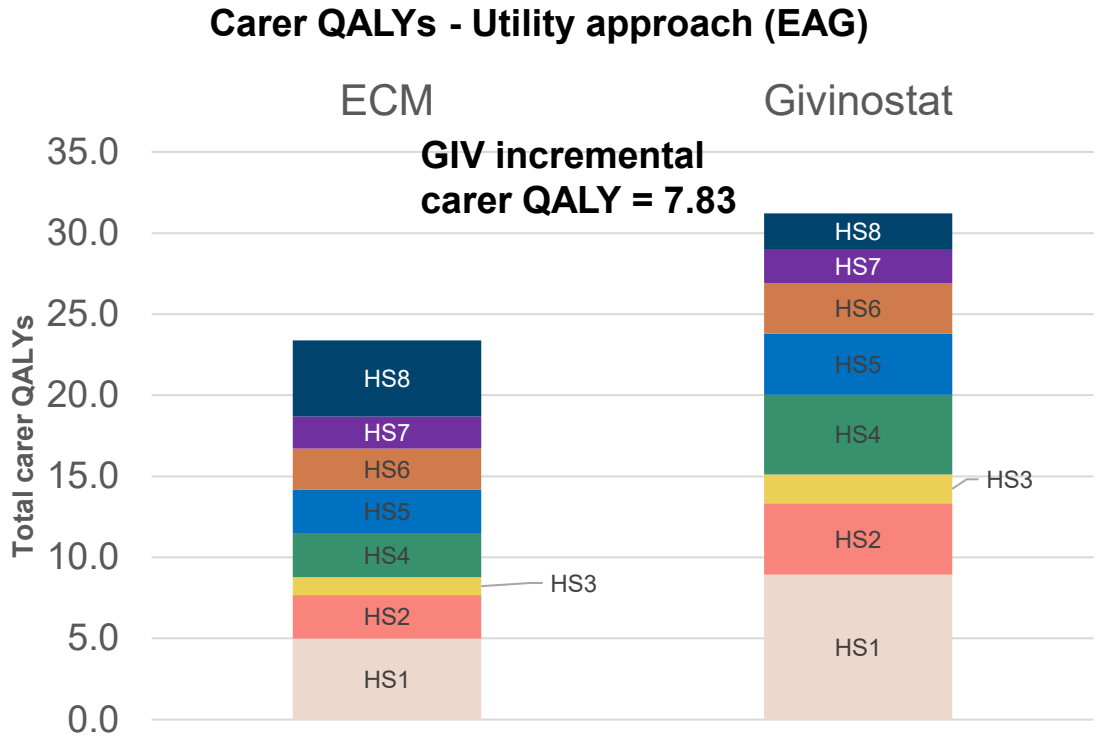
Key issues link

Carer HRQoL: Approaches - visual representation

Intro carer HRQoL

Utility approach vs Increments to midway results in more GIV incremental QALYs*





- Aim of slide is to visually show how approaches accrue carer QALYs (so no modelling of state 9 included)
- Increments to midway approach only applies carer utility to incremental time in HS (so no ECM)
- Sheffield 1 applies increment of 0 to health states 4 to 8 so effectively no carer utility is modelled for those states
- Please be aware of different scales on the two graphs

NICE

Abbreviations: BC, base-case; HRQoL, Health Related Quality of Life; GIV, givinostat; QALY, quality adjusted life year.

Notes: *, Approaches presented using company BC but with Sheffield 3 & no modelling of state 9.

Key Issue: Carer HRQoL - Approach

Key issues link
Intro carer HRQoL

Company's and EAG's use different approach to modelling

Stakeholders

- Sheffield data showed carers reporting anxiety and depression across all disease stages. Values in later stages may suggest shift from acute anxiety to chronic sadness, grief and fatigue.
- These emotional states directly reduce HRQoL. They affect sleep, relationships, mental health, and the ability to participate in society. They are compounded by the knowledge that Duchenne is a progressive, fatal condition.
- The financial impact of caring for a child DMD is profound.
- Many parents have to leave employment to become full-time carer.
- As DMD progresses into later stages, caregiving role becomes increasingly complex, intensive, and system dependent. Carers are not only responsible for direct disease-related tasks (e.g. ventilation, medication, transfers), but often manage wide range of indirect responsibilities, ensuring 24 hrs round the clock care.

"Carers are not only managing the physical and emotional demands of care—they are fighting for time, for quality of life, and for the chance to delay the inevitable. The tension between hope and grief, between advocacy and helplessness, defines the emotional landscape of Duchenne caregiving."

"I left two well-paid jobs because I couldn't manage the caring alongside full-time work. My marriage broke down. I am now divorced and in significant debt. I've attended more funerals of [his] friends than birthday parties."

Which approach to modelling carer HRQoL does the committee prefer?

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, external assessment group; HRQoL, Health Related Quality of Life; HS, health state; HTMF, hand-to-mouth function. **Links**: Equality issue slide summarises issues raised by stakeholders. Exemplars of previously used approaches slide.

Key issues link
Intro carer HRQoL

Carer HRQoL - Life extension on carer HRQoL

Company and EAG disagree on how to model carer HRQoL in state 9

Company:

- Assigned utility of zero for state 9. This effectively applies an increment of [redacted] to each carer for each life year gained with givinostat.
- No guidance on how caregiver outcomes should be valued, company approach is pragmatic solution.
- Uses Sheffield 1 data and models 3 carers, results in negative decrement for state 9 and GIV incremental carer QALY of 10.51.

State 9	Utilities	Increments to midway
Anchor	NA	[redacted] = HS4 (HS-HS4)
Death Utility	0	[redacted]
EAG scenario - 0.224 decrement for 3 years	NA	-0.224

EAG:

- Consider utilities approach avoids the carer QALY trap and already incorporates an extension to life benefit, so no additional modelling is necessary.
- As zero utility is applied for state 9, assumptions affecting state 9 have no effect on the ICER with the "utilities" approach.
- Consider company approach is not evidence based and may not be appropriate.
- Present evidence-based scenario with a bereavement disutility as observed in a perinatal study:
  - QALY loss of -0.224 for 3 years (using Sheffield 1 and assuming 3 carers).
  - This results in GIV incremental QALY of 0.01.

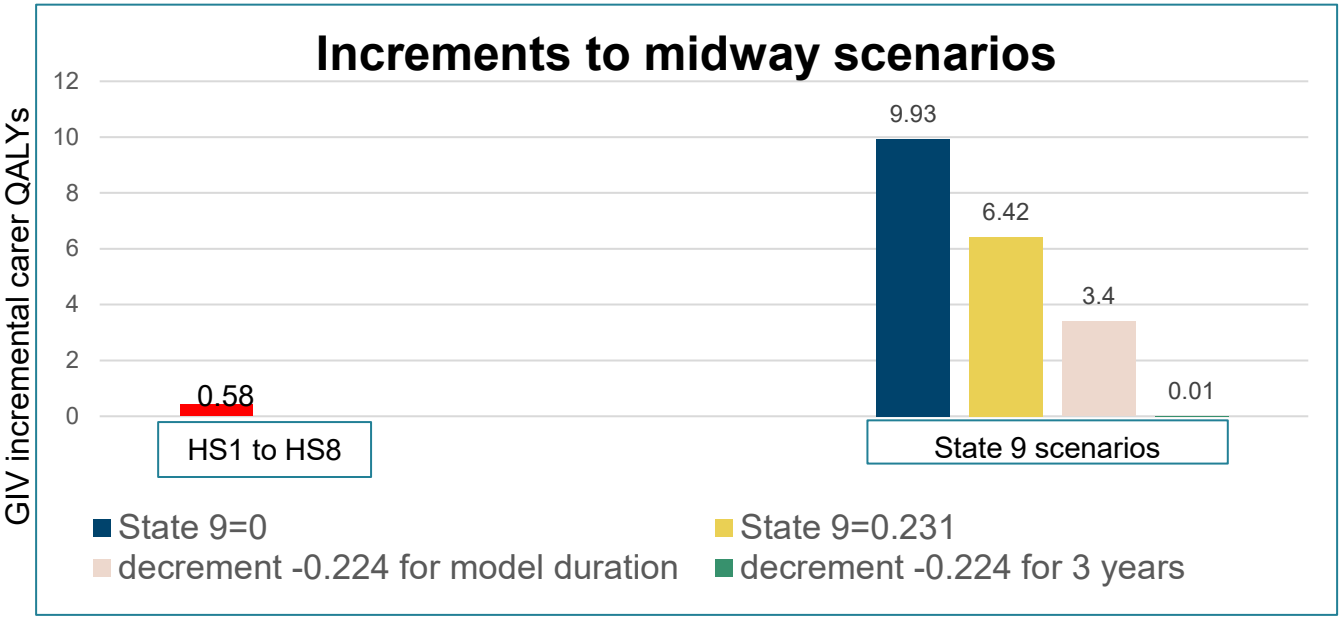
NICE

Abbreviations: HRQoL, Health Related Quality of Life; EAG, external assessment group; GIV, givinostat; HS, health state; QALY, quality adjusted life year.

Key issues link

Carer HRQoL: Life extension on carer HRQoL scenarios

Illustrative scenarios using Sheffield 1 & 2/3 carers per HS as in company BC



Company base case

- GIV incremental carer QALY: **10.51** (**9.93** in state 9 & **0.58** QALYs in HS1-8)
- Using utility approach with company base case gives **7.64** incremental carer QALYs (not shown on graph)
- EAG scenario - QALY loss of -0.224 for 3 years: results in incremental carer QALYs of 0.59 (**0.01** in state 9 and **0.58** in HS1-8)

NICE Technical team exploratory scenarios

1. Utility in state 9 of 0.231 (25% of general population utility), gives a state 9 increment of -0.423 and 6.42 incremental carer QALYs (Yellow bar).
2. Apply the -0.244 decrement for model duration giving 3.4 incremental QALYs in state 9 (Pink bar)

- Company's approach to modelling life extension on carers HRQoL (Blue bar) results in more incremental carer QALYs for GIV than when using decrement of -0.224 for whole duration of model (Pink bar).

Abbreviations: BC, base case; EAG, external assessment group; ECM, established clinical management; GIV, givinostat; HRQoL, Health-related quality of life; HS, health state; QALY, quality adjusted life year.

Key issues link
Intro HRQoL

Key Issue: Carer HRQoL - Life extension on carer HRQoL

EAG: modelling state 9 is not needed with utility approach; consider company approach not evidence based
Company: assumes zero utility for state 9, consider modelling of life extension effect on carers is appropriate.

Stakeholders

- When individual dies, caregiving responsibilities may cease, but the impact on HRQoL does not, the loss is not 'release' - it is trauma.
- A bereavement disutility should be included for state 9, informed by expert and carer insight.
- The HRQoL decrement associated with losing a child is not adequately captured in current models.

"The psychological damage this disease has caused me is profound. I have lost my sense of self, my career, my relationships, and my health. I have lived in a state of chronic grief, anticipatory loss, and relentless vigilance. There is no respite. Even joy is tinged with fear—knowing that every milestone might be his last."

"In my experience, the loss of a child with DMD often has devastating and life long impacts on carers. Sadly I have supported at least 1 family where a parent has taken their own life after the death of their child and several others where the family unit has broken down with significant negative impact on carers and siblings."

How should any extension to life benefit be accounted for in the modelling?

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, external assessment group; HRQoL, Health Related Quality of Life; HS, health state; HTMF, hand-to-mouth function.
Equality issue slide summarises issues raised by stakeholders.

Carer HrQoL: Summary and Key questions

Key issues link

Intro carer HRQoL

Parameter	Company	EAG	Key question
Source of caregiver HRQoL	Sheffield 1 (same value for HS4 to HS8)	Sheffield 3 (same value for HS5 to HS8)	What carer utility set is preferred for decision making?
Number of caregivers modelled	2 in ambulatory states, 3 in non-ambulatory states	1 in ambulatory states, 2 in non-ambulatory states	How many carers should be modelled in ambulatory and non-ambulatory health states?
Approach to implementing caregiver HRQoL in the model	Increments from midway health state	Utilities	Which approach to modelling carer HRQoL does the committee prefer?
Modelling of life extension benefit	Applies extension to life benefit [redacted] to incremental life years gained.	Considers the utility approach (with utility of 0 in state 9) implicitly models an extension to life benefit	How should any extension to life benefit be accounted for in the modelling?

Abbreviations: HRQoL, Health Related Quality of Life; HS, health state; EAG, external assessment group.

Key issues link

Resource cost: limited information available in literature

EAG and company differ in choice of studies to inform costs

- At ACM1 both company and EAG used Morgan 2024.
- Appendix slide summarises BOI and Morgan studies.

CfE: Requested scenarios explore tertiary-care & medical-aid costs and differentiate between HS 7 and 8.

Company

- Uses Morgan as it is most recent, UK-specific, and robust source aligned with the NICE reference case, showing expected cost increases across disease stages.
- BOI not appropriate as it is too small and uncertain.
- explored inclusion of tertiary care and medical aids costs and differentiating HS7/8 during clarification.

EAG

- Prefers to use BOI is it matches with model stages
- Notes model did not account for differences between treatment and ECM, unlike as in TA1031 and HST22.
- During clarification, company added administration and monitoring costs to reflect differences between GIV and ECM, but question remains “are these reflective of resources needed to treat with GIV?”
- Similarly, routine monitoring of bone health and endocrinology not modelled.
- Treatment related adverse events, DMD related comorbidities and adverse events of special interest known due to the use of corticosteroids not captured in the company’s model.
- Due to limitations with literature, model does not fully capture the health state costs.

Abbreviations: BOI, burden of illness; DMD, Duchenne muscular dystrophy; UK, United Kingdom; HS, health state; CfE, Call for Evidence; EAG, external assessment group; ECM, established clinical management; GIV, givinostat.

Key issues link

Resource cost: stakeholders

Company's and EAG's choice of estimating costs differ

Stakeholders

- Number of stakeholders question if cost in later stages is underestimated
- Concerns on resource implications to healthcare system beyond drug cost if givinostat is recommended
- All agreed there is a large difference between state 7 and 8.
- Suggested to combine qualitative insights with expert opinion and available data to reflect the real-world impact of disease progression.

Annual cost estimates in most advanced stages	
Patient testimony	£380,000 - 2-to-1, 24/7 care
Patient testimony	£250-300k - full ventilation £40-100k - night ventilation
Duchenne UK	>£200,000

"Currently I am in the full ventilation state and require round-the-clock care from two personal assistants. This includes waking nights. It is critical that there is always a carer with me as a ventilator malfunction or disconnection could otherwise mean death. The overall cost of my care package is around £250-300k per year….

On night ventilation, during the day I didn't require round-the-clock care, and could be left on my own for several hours during the day. Overnight, I didn't require waking night care, and a carer sleeping nearby was sufficient in the event of any difficulties. This meant significantly lower costs for care staff and varied as my condition progressed - from approximately £40k-£100k per year."

Abbreviations: EAG, external assessment group; QALY, Quality-Adjusted Life Year; SmPC, Summary of Product Characteristics.

Key issues link

Key issue: resource cost in model

Summary of company's and EAG's scenarios for annual cost in model

	Direct medical costs			Exploring tertiary-care & medical-aid costs +differentiate HS 7 & 8			
HS	Company case: Morgan 2024	EAG case: BOI - TA 1031	Company scenario: BOI	Company multiplier 3.05x to company BC	Company multiplier 1.3x to company BC - HS8	EAG multiplier 1.57x to EAG BC	EAG multiplier 30x to EAG BS - HS 4-8
1	£3,298	£7,680	£5,592	£10,068	£3,298	£12,058	£7,680
2		£3,391	£3,097			£5,324	£3,391
3		£3,625	£3,592			£5,691	£3,625
4	£6,681	£2,472	£2,370	£20,397	£6,681	£3,881	£74,677
5		£3,507	£3,349			£5,506	£105,943
6	£9,843	£7,837	£8,430	£30,049	£9,843	£12,304	£236,749
7		£7,771	£7,978			£12,200	£234,755
8		£12,579	£10,506		£12,962	£19,749	£380,000

- Only EAG exploratory patient testimony new multiplier (£380,000/£12,579) have large effects on ICERs.
- Givinostat increases time spent in all HS except HS 8 (vs ECM) this can have unexpected effects on costs.

What approach to cost is preferred by committee?

Abbreviations: BC, case-case; BOI, Burden of Illness study; HS, health state; EAG, external assessment group; ECM, established clinical management. Equality issue slide summarises issues raised by stakeholders.

Cost-effectiveness results

Key issues link

Results: company's base case

Base case with 3.5 % discount rate is above range that NICE considers acceptable

Deterministic results: 1.5% discount rate to health outcomes only

Technologies	Total costs (£)	Total Patient QALYs	Total carer QALYs	Inc costs (£)	Inc QALYs	ICER (£/QALY)
ECM	£99,448	7	0	-	-	-
Givinostat	£[redacted]	12.1	18.2	£[redacted]	26.9	£[redacted]

Deterministic results with 1.5 % discount rate to both costs and outcomes:

Technologies	Total costs (£)	Total Patient QALYs	Total carer QALYs	Inc costs (£)	Inc QALYs	ICER (£/QALY)
ECM	£128,714	7		-	-	-
Givinostat	£[redacted]	12.1	18.2	£[redacted]	26.9	£[redacted]

Deterministic results with 3.5 % discount rate:

Technologies	Total costs (£)	Total Patient QALYs	Total carer QALYs	Inc costs (£)	Inc QALYs	ICER (£/QALY)
ECM	£99,448	6.1	0	-	-	-
Givinostat	£[redacted]	9.6	10.5	£[redacted]	16.6	£[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; QALY, quality adjusted life year. *,
Note: severity modifier of 1.7 is applied to all results
Notes: *, using 1.5% non-reference discount rate to health outcomes;

Key issues link

Results: EAG preferred base case

EAG preferred base case is above range that NICE considers acceptable

Probabilistic results:

Technologies	Total costs (£)	Total Patient QALYs	Total carer QALYs	Inc costs (£)	Inc QALYs	ICER (£/QALY)
ECM	£106,699	7.37	14.13	-	-	-
Givinostat	£[redacted]	9.82	16.57	£[redacted]	5.39	£[redacted]

Deterministic results:

Technologies	Total costs (£)	Total Patient QALYs	Total carer QALYs	Inc costs (£)	Inc QALYs	ICER (£/QALY)
ECM	£106,699	7.36	14.13	-	-	-
Givinostat	£[redacted]	9.82	16.57	£[redacted]	5.40	£[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; QALY, quality adjusted life year.
Note: all results are using reference case discount rate of 3.5% to costs and health outcomes
Note: EAG's base case incorporates severity modifier of 1.2 not 1.7 as BOI study is used for patient utilities and reference discount rate is applied (se Patient utilities slide for more info. If 1.7 modifier was applied, ICER would be about £[redacted]/QALY smaller, but still above range that NICE considers acceptable.

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Key issues link

Managed access

Criteria for a managed access recommendation

Problem: no NIV or FVC <1L data for givinostat, therefore givinostat data were extrapolated using ECM data from givinostat LOA - resulting in high uncertainty in givinostat clinical effectiveness. Non-ambulant starting population was not considered in company submission.

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

- There is currently no proposal for managed access from company.

Is givinostat suitable candidate for managed access recommendation,
are there evidence gaps to address, data sources, and time in data collection?

Abbreviations: UK, United Kingdom; ECM, established clinical management; LOA, loss of ambulation; NIV, non-invasive ventilation.

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

- ❑ Recap from ACM1
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ✓ **Summary**

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Key issues

Key issues link - summary

Issue	Modelling and assumptions around & link	Effect
1. Population	Evidence and modelled population is not full MA population	Unknown
2. Givinostat treatment effect	Estimation, post-LOA effect and application in model	Large
3. Non-reference discount rate	Which discounting rate to use	Large
4. Patient HRQoL	Patient utility source & differentiate HS 7 and 8	Large
5. Carer HRQoL	Carer utility source & differentiate HS 7 and 8	Large
6. Carer HRQoL	Number of carers	Large
7. Carer HRQoL	Approach to modelling	Large
8. Carer HRQoL	Life extension on carer HRQoL	Large
9. Resource cost	Tertiary-care and medical-aid costs & differentiate HS 7/8	Moderate

Resolved issue	Committee's preferred conclusions/assumptions
Comparators	ECM comparator based on treatment regimens used in EPIDYS
ECM data for MAIC	UK real-world dataset
Givinostat data for MAIC	Full givinostat population from EPIDYS and OLE study (n=224)
HERCULES NHM survival	Company's updated NHM suitable for decision- making

NICE **Abbreviations**: HRQoL, health Related Quality of Life; HS, health state.

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

Supplementary appendix

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ACM1 slide: Equality considerations

Equality consideration

Potential issues identified during scoping and in stakeholders submissions

- DMD affects both children and young adults. Age is protected under the Equality Act.
- Presentations in girls can occur but are rare. Givinostat trials did not recruit any female participants. Sex is a protected characteristic under the Equalities Act.
- Some people have poor outcomes because of learning or behavioural difficulties, ADHD, autism, and pre-existing psychiatric difficulties, making up around 30% of the adult population.
    - A significant proportion of people cannot have CCS because of these issues and have worse outcomes. Therefore, this subgroup may not have access to givinostat if it is approved, increasing inequality of access to care.
    - Some can also have issues with North Star Ambulatory Assessment and other assessments as well as increased blood tests. This should not affect access to givinostat.
- Access to a specialist assessment and treatment centre due to location, mobility or transport issues can be major issue and could affect access to givinostat.

Are there any equality issues that the committee should consider?

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CCS, corticosteroids.

Treatment effect estimation: company's new evidence

Evidence from studies using steroid-treated and untreated patients

Bach and Martinez 2010	Untreated mean, years (N=117)	AF untreated	Observed treated mean, years (N=17)	AF treated	Treated mean estimated using untreated AF
LOA	9.7	-	10.8	-	-
NIV	19.2	1.98	22.9	2.12	21.4 (less than observed)
FVC<1L	21.9	2.26	28.9	2.68	24.4 (less than observed)

Trucco et al 2020:	Untreated mean, years (N=22)	AF untreated	Observed treated mean, years (N=252)	AF treated	Treated mean estimated using untreated AF
LOA	10.5	-	12.5	-	-
FVC<1L	13.2	1.26	16.1	1.29	15.7 (less than observed)

Company:

- While it is not possible to separate delay in LOA from ongoing effect of treatment with steroids beyond LOA, this shows that actual benefit (treated mean and AF) exceeds estimated mean with untreated AF.
- This reinforces that AF approach may underestimate the GIV treatment effect

EAG:

- Agrees it is impossible to separate treatment effect but does not consider this to support AF approach
- Prognostic factors between groups are not balanced and some are very small suggesting high uncertainty
- All treated and untreated AFs are higher or lower than UK RWE AFs (1.50 & 1.94) and not representative of ECM.
- Maintains use of AF overestimates GIV treatment effect.

Abbreviations: AF, acceleration factor; FVC<1L, forced vital capacity less than 1 litre; LOA, loss of ambulation; NIV, non-invasive ventilation.

Exploring treatment effects beyond LOA

GIV treatment effect: mean ages per health state

Median age for GIV discontinuation is lower that median age at NIV

Mean age, undiscounted years	Company - GIV	EAG - GIV	ECM
1. Early ambulatory	13.74	13.66	9.86
2. Late ambulatory	18.13	18.00	12.07
3. Transfer	20.13	19.98	13.10
4. HTMF, no ventilation	**24.44**	**22.76**	**14.87**
5. No HTMF, no ventilation	34.49	29.91	19.63
6. HTMF, night-time ventilation	32.91	28.61	19.62
7. No HTMF, night-time ventilation	37.81	32.05	21.78
8. Full-time ventilation	43.33	38.24	28.48
9. Death	55.23	53.98	50.50

EAG:

- Median age at GIV discontinuation is 22.58 years and 21.92 years in company and EAG model respectively
- Acknowledge that there may be some continued TxE beyond LOA, and even beyond discontinuing treatment, but assuming constant TxE indefinitely for a patients' lifetime that is independent of whether patients are receiving treatment or not is clinically implausible.
- EAG base-case attempts to align TxE in model expected HS average patient would be in when they discontinue treatment – HS 4 (mean age 22.76 in EAG base-case)

NICE

Abbreviations: EAG, external assessment group; GIV, givinostat; HS, heath state; HTMF, hand-to-mouth function; LOA, loss of ambulation; NIV, non-invasive ventilation; TxE, treatment effect.

Patient health-related quality of life: utility values

Company's and EAG's choice of observational studies differ

CfE: Requested to capture the increasing impact on patients as the condition progresses and explore different ways to differentiate between health states 7 and 8 for all possible sources.

Utilities	Company: Audhya 2023	EAG: BOI	Scenario: Landfeldt 2017 GLM 2	Not used: Landfeldt 2017 GLM 2 & 3	Scenario: Crossnohere 2021
1. Early ambulatory	0.79	0.70	0.70 →	0.70	0.65
2. Late ambulatory	0.64	0.49	0.61 →	0.61	0.49
3. Transfer	0.64	0.38	0.61 →	0.61	0.49
4. HTMF, no ventilation	0.28	0.54	0.22 →	0.22	0.31
5. No HTMF, no ventilation	0.25	0.51	0.22 →	0.22	0.31
6. HTMF, night-time ventilation	0.26	0.53	0.22	0.13 (GLM 3)	0.31
7. No HTMF, night-time ventilation	0.14	0.52	0.15	0.13 (GLM 3)	0.26
8. Full-time ventilation	0.14 [0.06]*	0.33	0.15 [0.06]*	0.05 (GLM 3)	0.26 [0.10]*

- All scenarios can use multiplier to differentiate between HS 7 & 8 [in brackets]* with minimal impact on ICERs
- See Crossnohere and Landfeldt studies for disease states and how they are assigned to HSs.
- See Audhya slide for information on states reported in paper and number of responses per HS
- See BOI slide for information on states reported in paper and number of responses per HS

NICE

Abbreviations: EAG, external assessment group; HRQoL, Health Related Quality of Life; HS, health state; HTMF, hand-to-mouth function.
Note: *, values in bracket indicate alternative value with the use of multiplier.
Note: Landfeldt 2017 mapped values from Landfeldt 2014/16 to published generalised linear regression models (GLM) and adjusted for number of effects (e.g. income class): for more see Patient utilities summary appendix slide.

Patient HRQoL: Crossnohere and Landfeldt studies

	Disease state	Crossnohere 2021	Landfeldt 2014/16	Landfeldt 2017	Model HS Ambulatory models	Model HS Landfeldt 2017 (GLM2 & 3)
Ambulatory model	Early ambulatory	0.65	0.75	0.70	HS 1	HS 1
	Late ambulatory	0.49	0.65	0.61	HS 2 to 3	HS 2 to 3
	Early non-ambulatory	0.31	0.24	0.22	HS 4 to 6	HS 4 to 6
	Late non- ambulatory	0.26	0.15	0.15	HS 7 to 8	-
Ventilation model	No ventilation	-	-	0.52	-	-
	Night - time ventilation	-	-	0.13	-	HS 7
	Full - time ventilation	-	-	0.05	-	HS 8

- Landfeldt 2017 mapped values from Landfeldt 2014/16 (included for info, but not utilised in model) to published generalised linear regression models (GLM) and adjusted for number of effects (e.g. income class).
- Company model utilises scenario using GLM 2. Scenario GLM 2 & 3 is not included even though it was requested during CfE and is used in company's scenario for carer HRQoL .
- See Audhya slide for information on states reported in paper and number of responses per HS
- See BOI slide for information on states reported in paper and number of responses per HS

Abbreviations: BOI, Burden of Illness Study; CfE, Call for evidence; HRQoL, Health Related Quality of Life; HS health state.

Patient HRQoL: Audhya 2023

Company matched Audhya utilities to model health states

Health states			N	EQ-5D-5L (mean SD)	Model	
Early ambulatory			11	**0.79 (0.20)**	**HS 1 n=11**	**0.79**
Preserved upper limb	no daytime ventilation	without symptomatic CM	10	0.84 (0.13)		
Mildly impaired upper limb	no daytime ventilation	without symptomatic CM	1	0.30 (NA)		
Late ambulatory			8	**0.64 (0.30)**	**HS 2&3 n=8**	**0.64**
Preserved upper limb	no daytime ventilation	without symptomatic CM	6	0.59 (0.33)		
Mildly impaired upper limb	no daytime ventilation	without symptomatic CM	2	0.79 (0.16)		
Early non-ambulatory			21	0.31 (0.13)	**HS4 n=34**	**0.28**
Preserved upper limb	no daytime ventilation	without symptomatic CM	2	0.46 (0.10)		
Mildly impaired upper limb	no daytime ventilation	without symptomatic CM	16	0.30 (0.14)		
Mildly impaired upper limb	no daytime ventilation	with symptomatic CM	3	0.29 (0.07)		
Late non-ambulatory			23	0.22 (0.15)		
Moderately impaired upper limb	no daytime ventilation	without symptomatic CM	9	0.22 (0.15)		
Moderately impaired upper limb	no daytime ventilation	with symptomatic CM	4	0.27 (0.08)		
Moderately impaired upper limb	nighttime & daytime ventilation	without symptomatic CM	5	0.25 (0.14)	**HS5 n=5**	**0.25**
Loss of upper limb function	no daytime ventilation	without symptomatic CM	1	0.26 (NA)	**HS6 n=1**	**0.26**
Loss of upper limb function	nighttime & daytime ventilation	without symptomatic CM	2	0.26 (0.01)	**HS 7&8 n=5**	**0.14**
Loss of upper limb function	nighttime & daytime ventilation	with symptomatic CM	2	0.02 (0.34)		

Abbreviations: CM, cardiomyopathy; HRQoL, Health Related Quality of Life; HS, health state.

Links: Crossnohere and Landfeldt studies & BOI slide for information on states reported.

Patient HRQoL issue

Patient HRQoL: BOI

Small unpublished study collected DMD-QoL in 24 patients

Utilities	BOI	Number of responses per HS
1. Early ambulatory	-	0: 0.70 used from Landfeldt 2017 GLM 2 in model
2. Late ambulatory	0.49	1
3. Transfer	0.38	2
4. HTMF, no ventilation	0.54	2
5. No HTMF, no ventilation	0.51	8
6. HTMF, night-time ventilation	0.53	5
7. No HTMF, night-time ventilation	0.52	4
8. Full-time ventilation	0.33	2

- Although BOI is aligned with model HS is has incomplete and limited data for individual disease stages
- Values not always aligned with the expected increasing impact on patients as the condition progressed:
  - Values in non-ambulatory HS 4 to 7 (0.51 to 0.54) are higher than values in HS 3 transfer (0.38)
  - Lower value for HS 2 (late ambulatory, 0.49) than HS 4 to 7 (0.51 to 0.54)

NICE

Abbreviations: DMD-QoL, Duchenne Muscular Dystrophy – Quality of Life; BOI, Burden of Illness Study; HRQoL, Health Related Quality of Life; HS, Health State

Links: Crossnohere and Landfeldt studies & Audhya slide for information on states reported in paper.

Patient utilities slide

Severity modifier

Most models' calculations results in result severity weighting of 1.7

Background
- Result can differ based on data source and discounting (see QALY weighting for severity for more info) .

Company
- Used Audhya 2023 for patient utilities.
- Non-reference 1.5% discount rate for health outcomes from year 30 onwards.
- Severity modifier of 1.7 in all scenarios – including reference discounting rate of 3.5% for the whole horizon.

EAG
- Used BOI study for patient utilities.
- Reference case discounting rate of 3.5% applied for the whole horizon.
- Severity modifier of 1.2.

TA1031
- Recent appraisal in DMD noted uncertainty in severity calculations
- Accepted severity modifier of 1.7

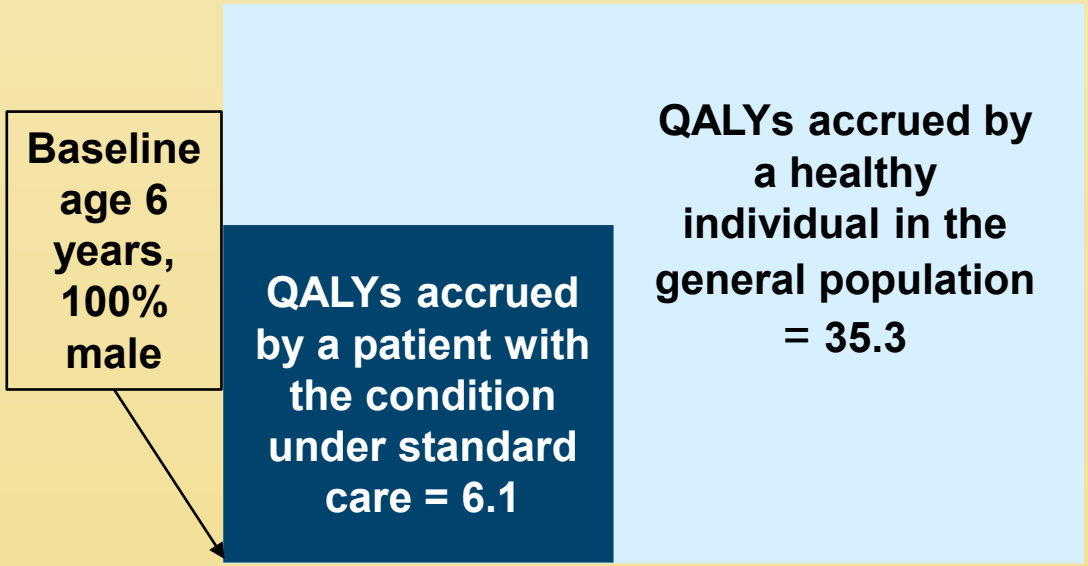
Abbreviations: BOI, Burden of Illness study; DMD, Duchenne muscular dystrophy; EAG, external assessment group.

ACM1 slide: QALY weighting for severity

Patient utilities slide

Company's and EAG's calculations provide different results

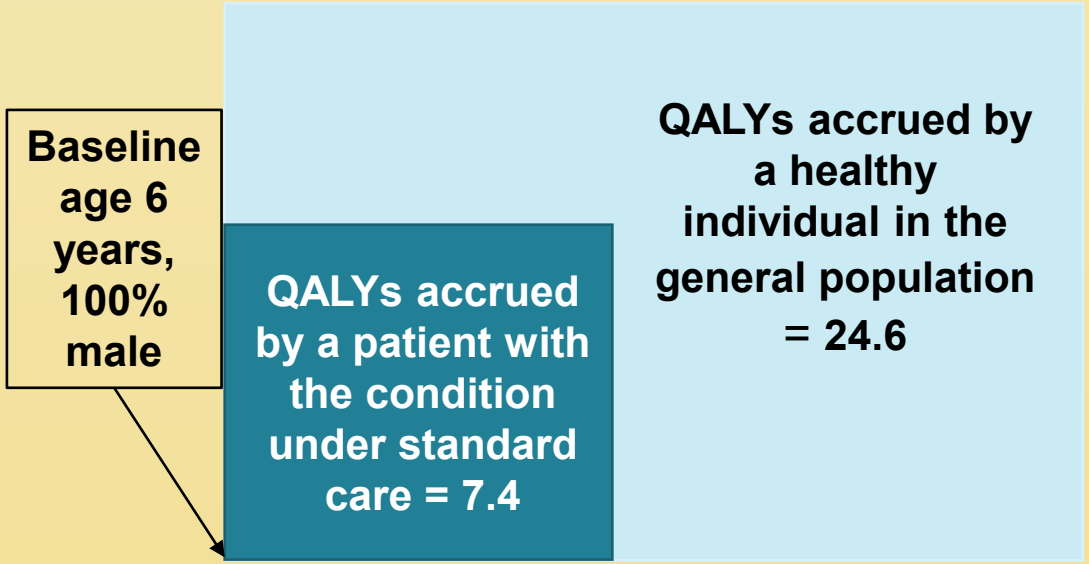
Company - 1.5% discounting from year 30 onwards & Audhya 2023 patient utility:



Absolute shortfall =
35.3 – 6.1 = 29.2 ➡ **x1.7**

- If baseline age 10: 27.7 ➡ **x1.7**
- If 3.5% discounting & age 10: 18.0 ➡ **x1.7**

EAG - 3.5% discounting & BOI patient utility:



Absolute shortfall =
24.6 – 7.4 = 17.2 ➡ **x1.2**

- If baseline age 10: 16.8 ➡ **x1.2**
- If 1.5% discounting & age 19: 26.3 ➡ **x1.7**

- Proportional shortfall <0.85 in all calculations ➡ x1

NICE **Note:** thresholds for absolute shortfall (12 to 18, x1.2; at least 18, 1.7x); thresholds for proportional shortfall (0.85 to 0.95, x1.2; at least 0.95, 1.7x)
Abbreviations: DMD, Duchenne muscular dystrophy; EAG, external assessment group; QALY, quality-adjusted life-year; SoC, standard of care.

Patient HRQoL: DMD QoL survey in clinical practice in Leeds

DMD QoL Survey

- DMD QoL: 14 questions exploring physical, social and psychological HRQoL (max score is 42)
- over 8 months in August 23 to April 24
- DMD patients attending clinics in Leeds
- [redacted] responses from [redacted] patients*

State	N	Reported by	n	Median (range)
Early ambulatory	[redacted]	DMD patients	[redacted]	[redacted]
		Carers	[redacted]	[redacted]
Late ambulatory	[redacted]	DMD patients	NR	[redacted]
		Carers	NR	[redacted]
Transitional	[redacted]	DMD patients	NR	[redacted]
		Carers	[redacted]	[redacted]
Non ambulatory	[redacted]	DMD patients	[redacted]	[redacted]
		Carers	[redacted]	[redacted]
Non ambulatory +nocturnal NIV	[redacted]	DMD patients	[redacted]	[redacted]
		Carers	[redacted]	[redacted]

[redacted]

Results for matched patient/carer pairs (data not presented):

- significant difference between carer (proxy) and patient scores in early and late ambulatory stage (mainly in physical domain), with carers having greater concerns for their child QoL.
- Responses were more similar at later disease stages

Abbreviations: DMD QoL; Duchenne Muscular Dystrophy Quality of Life; HRQoL, Health Related Quality of Life; NIV; not-invasive ventilation.
Notes: *, larger number of responses reflect the fact that for some patient their disease has progressed during the survey

Carer HRQoL: key studies summary

Carer HRQoL - source

	Sheffield study – new	Landfeldt 2017
Tool used	EQ-5D-5L	EQ-5D-3L
Sample size	N= [redacted]	N=770 (including 191 UK patients)
Tool filled by	Carers to DMD patients • [redacted] • [redacted]	Carers to DMD patients • 44 years (SD=8) • 79% female
DMD patients	[redacted]	14 years (range 5-43)
Health states (HS)	3 in main analyses: ambulatory, transfer & non-ambulatory. 8 in scenario.	4: early & late ambulatory, and early & late non-ambulatory.
Responses per HS	[redacted] in main analysis; [redacted] in scenario.	154 to 256
Location	UK	Germany, Italy, UK, US
Value set used	UK value set	UK value set
Ventilation: HS 7/8	Same values in main analysis ([redacted]). In scenario: HS7=[redacted] & HS8= [redacted].	Same utility values (0.79).

Abbreviations: DMD, standard deviation; EAG, external assessment group; EQ-5D-3L, European Quality of Life 5 dimensions 3 level version; HRQoL, Health Related Quality of Life; HS, health state; TTO, time to trade-off; SD, standard deviation; UK, United Kingdon, US, United States.

Carer HRQoL - source

Carer HRQoL: alternative source scenarios

Company and EAG use new unpublished Sheffield data, but have a different approach

Utilities	Company: Sheffield 1 HS4 to 8 are same	Scenario: Sheffield 2 (exploring non-ambulatory data)	EAG: Sheffield 3 HS5 to 8 are same	Scenario: Landfeldt 2017 (GLM 2 & 3)	Vignette – company ACM1
1. Early ambulatory	[redacted] →	[redacted] →	[redacted]	0.858	0.72
2. Late ambulatory	[redacted] →	[redacted] →	[redacted]	0.839	0.67
3. Transfer	[redacted] →	[redacted] →	[redacted]	0.839	0.58
4. HTMF, no ventilation	[redacted]	[redacted] →	[redacted]	0.784	0.56
5. No HTMF, no ventilation	[redacted]	[redacted]	[redacted]	0.784	0.50
6. HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]	0.775	0.54
7. No HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]	0.775	0.51
8. Full-time ventilation	[redacted]	[redacted]*	[redacted]	0.774	0.48

- Sheffield data do not differentiate between state 7 and 8.
- Key studies appendix slide - summarises Sheffield and Landfeldt studies characteristics

Abbreviations: EAG, external assessment group; GLM, generalised linear regression models; HRQoL, Health Related Quality of Life; HS, health state; HTMF, hand-to-mouth function; TE technical engagement.
Note: *, no values recorder for HS8, instead value was estimated from caregivers of boys requiring full-time ventilation while still retaining HTMF (n=2).

Carer HRQoL - approach

Carer HRQoL: Approaches and NICE appraisals

Approaches previously accepted by NICE appraisals

TA (year)	Disease area	Notes	Caregiver QoL committee conclusion
TA614 (2019)	Dravet syndrome	Company submitted disutilities	Accepted disutility modelling.
TA754 (2021)	Mycosis fungoides and Sezary syndrome (cancer)	Company had used an increment approach. But this was for a 3 state PSM with relatively mature survival data	Incorporate qualitatively due to lack of evidence and greater gain for carers than patients.
TA808 (2022)	Dravet syndrome	Company submitted utilities and disutilities approach	Use disutilities approach because utilities approach setting carer utility to 0 after patient death was implausible
HST22 (2023)	Duchenne Muscular Dystrophy	Company used a disutility approach.	Incorporate qualitatively as carer disutilities resulted in negative incremental QALYs for ataluren.
TA1031 (2025)	Duchenne Muscular Dystrophy	Company modelled carer disutility specifically for behavioural AEs.	Accepted behavioural AE modelling. No life extension was modelled for vamorolone so carer QoL had no effect beyond AEs.

NICE

Abbreviations: AE, adverse effects; HRQoL, Health Related Quality of Life; PSM, partitioned Survival Mode; QALY, quality adjusted life year.
Please note: Selection of examples only, not an exhaustive list of appraisals featuring caregiver QoL

Cost link

Resource cost: sources for direct medical cost

Problem: limited information in both BOI and Morgan studies

	Company: Morgan 2024 (Project HERCULES CPRD)	EAG: BOI 2020 - values used in TA1031 (Project HERCULES unpublished)
Population	Patients with muscular dystrophy. Excluded if they were female, Becker's dystrophy or >40 years.	Patients with DMD diagnosis at least 24 months before the index date
N	N=639	N=44/129
Health states	3: Ambulatory & non-ambulatory without/with ventilation	8: as in model
Included	Primary care, Prescriptions, Outpatient appointments, A&E attendances, Inpatient admissions.	Direct medical and non-medical cost and indirect cost

Note: Company provided Landfeldt 2014 and BOI scenarios model. Company's BOI scenario differs slightly from EAG's base case. In summary, TA1031 values also include cost of OTC medication, transport, transfer payments, alternative therapy, and other non-medical costs and different method was used to inflate values.
Links: for more info see Morgan 2024 and BOI TA1031 values slides.

Abbreviations: BOI, Burden of Illness study; EAG, Evidence Assessment Group; TA1031, Technology Appraisal 1031; OTC, Over-the-Counter.

Annual direct medical cost: Morgan 2014, CPRD study

Used in company's base case

	Ambulatory HS 1 to 3	Non-ambulatory & no ventilation HS 4 to 5	Non-ambulatory & with ventilation HS 6 to 8
N – patients	387	188	64
Primary care contacts	£176	£274	£429
Prescriptions	£460	£1,139	£3,582
Outpatient appointments	£1,398	£1,212	£1,083
A&E attendances	£55	£91	£123
Inpatient admissions	£841	£3,221	£3,531
Total costs	£2,931	£5,938	£8,748
Total inflated ID6323*	**£3,298**	**£6,681**	**£9,843**

Abbreviations: A&E, accident and emergency; CPRD, Clinical Practice Research Datalink.

Note: *,BOI costs based on 2018/19 prices. These have been uplifted to 2022/23 prices using the inflation indices in PSSRU 2023

Annual direct medical cost: EAG's uses TA1031 BOI values

Disease Stage	1	2	3	4	5	6	7	8
N – health systems	40	20	7	7	14	16	10	15
Procedure/Test	£2,507	£1,339	£712	£276	£1,873	£1,586	£1,324	£1,589
Medical device	£1,012	£348	£1,288	£648	£77	£4,886	£5,048	£6,670
Consultation	£1,145	£939	£1,025	£886	£917	£856	£552	£883
Hospitalisation	£0	£6	£0	£0	£0	£0	£0	£0
N - patients	15	2	3	3	8	5	4	4
Home alteration	£163	£63	£100	£253	£47	£8	£18	£0
OTC medication	£53	£222	£32	£20	£39	£22	£30	£550
Transport	£123	£0	£73	£100	£3	£35	£19	£2,363
Transfer payments	£101	£250	£150	£206	£430	£176	£514	£93
Alternative therapy	£910	£100	£120	£0	£0	£0	£0	£0
Other non-medical costs	£1,400	£8	£0	£0	£0	£0	£0	£0
Total	£7,416	£3,274	£3,501	£2,388	£3,387	£7,569	£7,505	£12,147
Total inflated ID6323*	£8,522	£3,763	£4,023	£2,745	£3,892	£8,698	£8,624	£13,960
Total inflated TA1031 – used in model as EAG preferred base- case**	**£7,679**	**£3,391**	**£3,625**	**£2,472**	**£3,507**	**£7,838**	**£7,771**	**£12,579**

Note: *,BOI costs based on 2018/19 prices. These have been uplifted to 2022/23 prices using the inflation indices in PSSRU 2023.
**, BOI cost inflated via OCED CPI index to 2023 prices