Vamorolone for treating Duchenne muscular dystrophy ACM2

For public – confidential information redacted

Technology appraisal committee C [4th June 2024]

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ACM 1 – draft guidance recommendation

Vamorolone is not recommended, within its marketing authorisation, for treating Duchenne muscular dystrophy (DMD) in people 4 years and over

- Committee concluded that it was not possible to establish a plausible cost-effectiveness estimate – further economic modelling was required

Vamorolone (Agamree, Santhera)

Technology details

Marketing authorisation	Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older MHRA granted Jan 2024
Mechanism of action	Differs from traditional glucocorticoids by its lack of an 11β hydroxy-carbonyl group, which alters structure and activity: 1. High affinity to glucocorticoid receptor with suppression of pro-inflammatory pathways 2. High affinity to mineralocorticoid receptor, potentially benefiting heart function 3. Membrane stabilisation and promotion of membrane repair
Administration	In people less than 40 kg, 6.0 mg/kg/day orally In people 40 kg and above, 240 mg (equivalent to 6 ml) once daily orally Daily dose may be reduced to 4 mg/kg/day, or 2 mg/kg/day based on individual tolerability

Price	• 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
	  • Vamorolone has a confidential commercial arrangement (simple PAS)

Abbreviations: kg, kilogram; mg, milligram; MHRA, Medicines and Healthcare products Regulatory Agency; ml, millilitre; PAS, patient access scheme; UK, United Kingdom.

Response to draft guidance consultation

- Company
- Muscular Dystrophy UK and Action Duchenne (joint response)
- Association of British Neurologists
- Clinical expert
- Web comments

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Key issues from ACM1 and company's response

Key issue ACM1	Committee preference	Addressed in response?
Comparators and treatment sequencing	• Remove basket of comparators • Explore the potential of treatment sequencing	Removed basket of comparators but no scenario on sequencing
Equal efficacy	• No robust evidence to suggest equal efficacy • Scenario assuming difference in muscle function based on VISION-DMD	Scenario provided with 5% and 10% lower efficacy for vamorolone
Long-term discontinuation rates for vamorolone	• Preferred EAG assumption (assumes proportion discontinuing vamorolone is the same as long term deflazacort CINRG data) but highly uncertain	EAG assumption included as base case
Dose reductions	• All treatments modelled same after dose reductions • Scenario - benefits are reduced after dose reduction in all treatment arms	Partially - Introduced HR approach using FOR-DMD data
Long-term growth and behavioural outcomes following vamorolone	• Requested alternative analysis of AEs and clarification that comparator AEs not overestimated. • Scenario with all VISION-DMD AEs	Provided new analyses
Face validity of patient and carer utility estimates	• Concerns with face validity – more analysis of carer HRQoL	Provided new analyses
Severity modifier (1.7x vs 1.2x modifier)	• 1.7x for patient QALYs only	Yes - 1.7x for patient QALYs only now company base case

New evidence in response to DG

Company addressed majority of requests in draft guidance and included new analyses

New analyses from company	ICER impact
Stopping rule – applied after nighttime ventilation is started	Large
Base case costs – changed from BoI study to Landfeldt et al. 2017	Large
Mortality data – changed the source of mortality data and increased the time horizon in the model from 50 years to 95 years	Small
Patient utility source changed to Landfeldt et al. 2023	Small
Carer disutility doubled to account for 2 carers per patient from loss of ambulation to death	Small

New evidence from patient groups
Patient survey conducted by MDUK and Action Duchenne

Abbreviations: BoI, burden of illness; DG, draft guidance; ICER, incremental cost-effectiveness ratio

Response to DG consultation (1/3)

Summary of responses from Muscular Dystrophy UK and Action Duchenne

Survey

- Ran survey (April 2024) in response to DG. Collected experience and impact of side effects associated with corticosteroid use
- Respondents [n=76, 88% parents or carers] answered questions on side effects: severity, interference on daily life, behaviour changes, and improvement in quality of life from side effect reduction
- Provided quantitative and qualitative responses showing the profound, wide-ranging impact corticosteroid use has on people and their families and carers
- EAG conducted analysis of responses (see slide 18) to assess the face validity of utility decrements applied to each AE
- Found that stunted growth, behaviour problems, weight gain, risk of fractures and osteoporosis, were the critical AEs for people with DMD and their carers.

Further comments:

- Concerned about cost of vamorolone and lack of access – parents fear that the high cost of vamorolone could pose significant challenges for healthcare systems, potentially limiting access for those who could benefit from it the most.
- Concerns about the clarity in the draft guidance around the efficacy of vamorolone

Abbreviations: AE, Adverse events; DG, draft guidance

"As parents when we are told about steroids being the only option to use, the consultants then tell us all the side effects … it is an impossible choice. "

"Our son is unable to tolerate the side effects of steroids and so has no treatment for his DMD. We were very much hoping that alternatives would be available this year".

"stunted growth and delayed puberty contribute significantly to social isolation."

Response to DG consultation (2/3)

Summary of responses from Stakeholders

Professional organisation (Association of British Neurologists) and clinical expert

Evidence base:

- No evidence that vamorolone is less effective than CS at stabilising muscle function and slowing decline in motor skills
- Clinical experience indicates that growth is preserved on vamorolone in comparison to other corticosteroids
- Agree with concerns around natural history model producing unrealistic life expectancy in patients

Line of treatment:

- DG did not address those who can't have prednisolone and have no alternate treatment options:
    - vamorolone should be compared against placebo for those patients
    - patients who stop steroid therapy have earlier greater ventilator needs and worse cardiac outcomes
    - more likely to have additional disabilities (equality issue)

Abbreviations: CS, corticosteroids; DG, draft guidance

Response to DG consultation (3/3)

Summary of responses from Stakeholders

Web comments

- Few treatment options available for patients
- Impact on individuals and families living with Duchenne is already devastating but burden of side effects with CS have a large impact on all aspects of life
- Need alternative treatments when prednisone and deflazacort have to be stopped
- Evidence shows vamorolone is as effective as CS without the burden of side effects

"Our son's Neuromuscular Consultants…are keen…to switch to Vamorolone…Our son wants to grow. He wants to attend University and have a career"

"sufferers of the disease… cannot receive the best available treatment in this country and must…go abroad to to be able to receive this treatment"

"My son…has…Zoledronic… infusions …and additional medication to treat his Osteoporosis. Imagine a world where this was not necessary - to not have to treat the negative side-effects of Deflazacort/ Prednisolone"

Abbreviations: CS, corticosteroids; DG, draft guidance

Equality considerations

NICE kept remit and population broad to be inclusive to all

At ACM 1 committee concluded that:

- Trial evidence only from boys aged 4 years and older - Committee recommendation does not restrict access for some people over others, the committee agreed that this was not a potential equalities issue
- Committee acknowledged that clinical expertise would usually be concentrated at a small number of centres
- Committee acknowledged there was interest in vamorolone for people who have had corticosteroid treatment

Professional organisation comment:

- Recommendation discriminates against patients with learning disabilities, ADHD, autism and pre-existing psychiatric difficulties (1/3 of population).
- These patients don't tolerate behavioural side effects of CS and more likely to discontinue. Discontinuation associated with higher morbidity and earlier mortality.
- Cohort should attract separate consideration. "We suggest specifically considering vamorolone use in this group when [prednisone and deflazacort] have to be discontinued."
- Harder to study in this group due to cognitive impairments which further increases their inequality of access to care

- What is the committee's view of the equalities issues relating to people with learning disabilities, ADHD, autism and pre-existing psychiatric difficulties?
- Are there any further potential equality issues the committee should consider?

Key issues for ACM2

Issue	ICER impact
Treatment sequencing	Unknown
Equal efficacy for vamorolone and corticosteroids	Small
Implementation of dose reduction	Large
Uncertainty in long-term adverse event outcomes	Unknown
Stopping rule	Large
Source of health state costs	Large
Patient utility estimates	Small
Carer disutility estimates	Small
Mortality and time horizon	Small

Other considerations
Managed access proposal
Equality considerations

Clinical effectiveness

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Treatment pathway for DMD

Key issue: Treatment sequencing

Evidence based on treatment-naïve population and no sequencing

Background

- Model did not allow people to switch CS and or stop and move onto vamorolone
- Committee acknowledged there was interest in vamorolone for people who have had corticosteroid treatment

Company response to DG

- VISION-DMD - switching from 0.75mg/kg of prednisone to 6mg/kg of vamorolone after 24 weeks results in retaining benefit in motor function endpoints.
- Ongoing trial VBP-006 study – found no patient switching from long-term CS developed any symptoms suggesting adrenal insufficiency after switching to vamorolone 6 mg/kg, including those patients with pre-existing adrenal suppression

Stakeholder comments

- Patients unable to take prednisone and deflazacort have highest unmet need, vamorolone would be useful
- Patients who stop steroid therapy have earlier and greater ventilator needs and worse cardiac outcomes

EAG critique

- Economic model not structured to allow people to have a sequence of glucocorticoid treatments for DMD

NICE

Does the modelling appropriately capture relevant treatment sequences?
What is the committee's view on treatment with vamorolone when CS treatment is not suitable?

Key issue: Equal efficacy for vamorolone and corticosteroids

Company provided evidence for equal efficacy of vamorolone and corticosteroids

Background

- Company believed data showed vamorolone had equal efficacy, based on lack of statistical significance between vamorolone and prednisone, EAG disagreed, citing numerical difference in all muscle function outcomes
- Committee concluded that there was no robust evidence to suggest equal efficacy and requested scenario assuming difference based on VISION-DMD data

Company response to DG

- Delphi panel suggest numerical difference in muscle outcomes observed in VISION-DMD is not clinically relevant
- Vast majority of patients cannot tolerate full dose of other CS long-term, reducing their overall efficacy
- Variation in results expected with small trial population, only pre-specified analyses should be considered
- Provided scenarios with 5% and 10% lower efficacy than other CS and HR of 1.075 for 4mg dose reduction

SH consultation response (clinical expert): No significant difference in the 2 groups (VISION DMD)

EAG critique

- Company rationale for percentage reduction appears arbitrary
- EAG clinical expert suggests trajectory in muscle function over 2-3 years is substantial and is not captured
- Point estimate analysis on the 5 muscle function outcomes from VISON-DMD suggests 32% reduction in efficacy
- 20% reduction in efficacy (the midpoint between EAG's and company's estimates) used in base case

NICE Should a reduction in efficacy with vamorolone be modelled to capture difference in muscle function?

Abbreviations: CS, corticosteroids; DG, draft guidance; DMD, Duchenne muscular dystrophy; EAG, external assessment group; HR, hazard ratio

Cost effectiveness

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Dose reduction slide ACM1

Key issue: Implementation of dose reduction

Company update implementation of dose reduction

Background

- In the original model SoC dose reduction impacted costs and benefits; vamorolone impacted only costs
- Committee concluded treatment effectiveness and tolerability should be modelled the same after dose reductions and requested a scenario with benefits reduced in all arms

Company response to DG

- Updated reduced-dose transition probabilities for vamorolone to be consistent with comparators
- Introduced a HR of [redacted] applied to transition probabilities for reduced dose CS - HR of 1 applied to vamorolone
- Applied reduction in AEs for CS when people down-titrate from full dose based on FOR-DMD
- Provided a scenario that reduces efficacy by 7% for vamorolone 4mg/kg versus 6mg/kg (based on PK model for down-titrated patients indicating [redacted])

EAG critique

- HR approach might overestimate progression on comparators - Model results are sensitive to the approach used (HR vs. EAG preferred: equal assumptions for all treatments)
- For SoC, reduction in AEs is taken from FOR-DMD for available events – for vamorolone and events with no data the mean reduction (18%) after dose reduction is applied – method should be the same in all arms
- No reduction in efficacy for vamorolone after dose reduction is not consistent with evidence
- PK data did not include people receiving vamorolone 4 mg/kg – efficacy reduction estimate not credible

What is the most appropriate method of modelling dose reduction?

Key issue: Uncertainty in long-term adverse event outcomes

Company provide further analysis of adverse event data

Background

- The company used VISION-DMD data at 24 weeks to inform moderate and severe AEs in the model
- The EAG highlighted this was short-term data, noting 6-year follow-up data for SoC
- The committee requested alternative analysis of AEs to clarify that comparator AEs were not overestimated
- The committee also requested a scenario with all VISION-DMD AEs

Company response to DG

- Provided reasons for vamorolone's reduction in risk of weight gain and cushingoid features, growth stunting, behavioural issues, fractures, cataracts, heart issues and puberty delay versus prednisone and deflazacort
- Evidence provided from long-term safety pool, VISION-DMD and FOR-DMD 6-month data, CINRG data, FOR-DMD 36 month and VBP15-LTE 30 months data, and steroid switching cohort data
- Base case updated to include all AESIs from VISION-DMD, mild AEs have 25% disutility of moderate/severe AEs

EAG critique

- Disutility modelling linked to AE rates issues with extrapolating sources over long term
- Assumption of 25% disutility of moderate/severe for mild AEs appears arbitrary – included a scenario with mild AEs having 50% disutility compared to moderate/severe AEs
- Reducing growth stunting is an important benefit of vamorolone, particularly compared to deflazacort

Is the company's updated approach to modelling AEs appropriate?

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Abbreviations: AE, adverse event; AESI, adverse events of special interest; DG, draft guidance; DMD, Duchenne muscular dystrophy; EAG, external assessment group; EAP, extended access programme; SoC, standard of care

Key issue: Uncertainty in long-term adverse event outcomes

EAG analysed patient survey by MDUK and Action Duchenne

- Survey provided valuable insight into the relative effects of AEs associated with steroids and their impact on daily living but could not provide any point estimates which could be used as inputs directly into the model
- Survey supports relative impact of behavioural issues and stunted growth as the most impactful AEs in the model
- Survey highlights frequency of behavioural issues is variable - of people with DMD, 61.1% experienced behavioural issues either 'often' or 'all the time'. The remaining 39.9% experienced it only 'some of the time', 'rarely' or 'not applicable' (assumed to be 'not at all')
- EAG notes this variability is not captured by company modelling. EAG approach (applying behavioural issues only for boys aged 4-12 [see slide 21]) partially accounts for this

EAG analysis of patient survey results compared with model inputs

Side effect	Mean rating (out of 5) based on patient survey in terms of		Model inputs (EAG)		
	Severity	Interference with daily activities	Moderate/severe AESI (cumulative incidence)		QALY loss per event
			Deflazacort	Prednisone	
Stunted growth	4.1	2.9	76.08%	43%	0.45
Behavioural issues (people with DMD)	3.6	3.1	8.93%	25.81%	0.09
Behavioural issues (carer)			-	-	0.16

Have behavioural issues been adequately captured in the modelling?

New analysis

Key issue: Stopping rule

Company include new stopping rule in response to DG

Background

- DG: “The company noted the possibility of a treatment stopping rule for vamorolone. But it did not provide any further details on the clinical rationale for this, criteria on which it could be based or on its appropriateness in practice. So, the committee could not consider any stopping rule”

Company response to DG

- Include a stopping rule with all patients receiving vamorolone until nighttime ventilation, following which no costs or benefits are applied to vamorolone patients
- Lack of robust data to demonstrate adequate benefits of continuing vamorolone once patients have started nighttime ventilation to overcome the risks
- Currently, there is no available data on the benefits or risks of vamorolone in patients on nighttime ventilation

EAG critique

- Excluded this assumption in its analyses – no justification from company
- Noted no stopping rule applied for SoC treatments
- EAG received feedback from one of their clinical experts:
  - Practice is to continue steroid usage
  - Growth likely to be completed before nighttime ventilation is started so may be less advantage for vamorolone
  - However, if patients have been on vamorolone they may be very reluctant to change

Should a stopping rule be applied for people receiving nighttime ventilation?

Key issue: Source of health state cost data

New analysis

Company change source of health state cost data in response to DG

Full cost data

Background

- Committee preference at ACM1: exclude growth hormone costs and non-reference case costs
- In the original CS, the company used a BoI study from Project HERCULES as the source for health state costs
- The company have updated the source of their base case costs to Landfeldt et al. 2017, which was previously included as a scenario

Company response to DG

- Landfeldt et al. 2017 was used in the NICE appraisal for ataluren in DMD (HST22) and no issues were raised
- Surgery costs were not captured in Landfeldt et al., 2017 the surgery cost for cataracts is now captured as part of the treatment for adverse events, following NHS reference costs 2021/22
- Growth hormone costs and non-reference costs removed

NICE technical team comments and EAG critique

- The costs included in Landfeldt et al. 2017 are much higher for each health state than the BoI study
- When combined with the proposed stopping rule, the incremental costs for vamorolone are greatly decreased
- It is unclear whether the costs included in Landfeldt et al., 2017 are all from the perspective of the NHS and PSS
- BoI study health states are better matched to model structure – Landfeldt et al. health states do not match model
- Costs of 2 endocrinologist visits added, unable to validate assumption in time (excluded from EAG base case)

New analysis

Key issue: Patient utility estimates

Company update utility source and utility assumptions in response to DG

Background

- Committee raised concerns with face validity of utility values (later states had higher values) and how disutility for behavioural issues had been implemented – requested health state utility values were plausible and robust

Company response to DG

- Changed health state utilities source to Landfeldt et al., 2023 based on feedback
- Changed length of behavioural issues decrement from 6 months to 18 months based on expert opinion
- Growth stunting duration changed from 1-year to 8-year duration based on clinical expert opinion
- 36.4% chance of loss of ambulation after fracture applied based on Yildiz et al 2020
- Disutility increased for spinal surgery from 1-year to 2-year duration based on expert opinion
- Disutility for cataracts added – applied for 1 month using cataract disutility value from HST11 (-0.142)

EAG critique

- BoI study aligns with health states used in the model, Landfeldt et al. does not – so EAG preferred BoI
- Not clear why the Landfeldt et al. utilities are more valid than the utilities from the BoI study
- EAG's clinical expert agrees with changes in length of behavioural issues and growth stunting decrements
- Clinical advice to EAG suggests that behavioural issues from CS would only apply to approximately age 12; continuing behavioural issues beyond this age will not be due to steroids
- Company assumed behavioural issues were equal in severity to severe side effects from anti-epileptic drugs (0.12 per year) - in absence of evidence, EAG preferred assuming disutility equal to moderate side effects (0.06)

Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; EAG, external assessment group; HST, highly specialised technology

Key issue: Patient utility estimates

Company update utility source and utility assumptions in response to DG

ACM1 utilities slide

New analysis

Updated company utility values and disaggregated QALYs*

Ambulatory class	Utility	Vam QALYs	Pred QALYs	Diff.
Early ambulatory	0.65	[redacted]	[redacted]	[redacted]
Late ambulatory	0.49	[redacted]	[redacted]	[redacted]
Transfer	0.49	[redacted]	[redacted]	[redacted]
HTMF, no ventilation	0.31	[redacted]	[redacted]	[redacted]
No HTMF, no ventilation	0.31	[redacted]	[redacted]	[redacted]
HTMF, night-time ventilation	0.26	[redacted]	[redacted]	[redacted]
No HTMF, night-time ventilation	0.26	[redacted]	[redacted]	[redacted]
Full-time ventilation	0.26	[redacted]	[redacted]	[redacted]
Total health state QALYs		[redacted]	[redacted]	[redacted]
Adverse events		[redacted]	[redacted]	[redacted]
Acute events		[redacted]	[redacted]	[redacted]
Carer QALYs		[redacted]	[redacted]	[redacted]
Total QALYs		[redacted]	[redacted]	[redacted]

Company uses Landfeldt et al. 2023 health state utilities

*company results include stopping rule

Updated EAG utility values and disaggregated QALYs

Ambulatory class	Utility	Vam QALYs	Pred QALYs	Diff.
Early ambulatory	0.70	[redacted]	[redacted]	[redacted]
Late ambulatory	0.49	[redacted]	[redacted]	[redacted]
Transfer	0.38	[redacted]	[redacted]	[redacted]
HTMF, no ventilation	0.54	[redacted]	[redacted]	[redacted]
No HTMF, no ventilation	0.51	[redacted]	[redacted]	[redacted]
HTMF, night-time ventilation	0.53	[redacted]	[redacted]	[redacted]
No HTMF, night-time ventilation	0.52	[redacted]	[redacted]	[redacted]
Full-time ventilation	0.33	[redacted]	[redacted]	[redacted]
Total health state QALYs		[redacted]	[redacted]	[redacted]
Adverse events		[redacted]	[redacted]	[redacted]
Acute events		[redacted]	[redacted]	[redacted]
Carer QALYs		[redacted]	[redacted]	[redacted]
Total QALYs		[redacted]	[redacted]	[redacted]

EAG use BoI health state utilities (as in ACM1)

Are values for patient utility and impacts of adverse events suitable for decision making?

Abbreviations: ACM, appraisal committee meeting; BoI, burden of illness; DG, draft guidance; diff., difference; HTMF, hand-to-mouth function; pred, prednisone; QALY, quality-adjusted life year; Vam, vamorolone

New analysis

Key issue: Carer disutility estimates

Company update carer disutility assumptions in response to DG

Background

- Committee not convinced that carer health-related quality of life had been modelled robustly – noted behavioural issues accounted for almost all carer quality-of-life gains

Company response to DG

- 2 caregivers applied to all non-ambulatory health states (4-8), with 2x decrements for those health states
- Changed length of behavioural issues decrement from 6 months to 18 months based on expert opinion which also applied to carer disutilities
- Carer disutility for behavioural issues sourced from Landfeldt et al. 2016 – 0.11 per year for total disutility of 0.16 over 18 months

EAG critique

- Landfeldt et al. model includes only 1 carer for all health states
- 2 carers for severe health states might be over estimating carer QALYs – 1 carer included for all health states in EAG base case
- The clinical advice to the EAG with regards to behavioural issues (CS-aggravated behavioural issues applying until the age of 12) should also apply to carer disutilities – applied to EAG base case

Abbreviations: CS, corticosteroids; DG, draft guidance; EAG, external assessment group

New analysis

Key issue: Carer disutility estimates

Company update carer disutility assumptions in response to DG

Carer utility loss as progress through health states from ACM1

Ambulatory class	Carer disutility
Early ambulatory	0
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

Carer QALY loss due to adverse/acute events from ACM1

Adverse events	QALY loss per event
Behavioural issues	-0.06

Disaggregated carer QALYs from ACM1

	Vamorolone	Prednisone
Sum of health states	-0.77	-0.76
Acute events	0.00	0.00
Adverse events	-0.05	-0.54
Total	-0.81	-1.31

Updated carer utility loss as progress through health states

Ambulatory class	QALY loss
Early ambulatory	0
Late ambulatory	-0.02
Transfer	-0.08
HTMF, no ventilation	-0.16 (with 2 carers)
No HTMF, no ventilation	-0.16 (with 2 carers)
HTMF, night-time ventilation	-0.16 (with 2 carers)
No HTMF, night-time ventilation	-0.10 (with 2 carers)
Full-time ventilation	-0.10 (with 2 carers)

Updated carer QALY loss due to adverse/acute events

Adverse events	QALY loss per event
Behavioural issues	-0.16 (-0.32 if health state 4+)

Updated disaggregated carer QALYs

	Vamorolone	Prednisone
Sum of health states	-0.90	-1.31
Acute events	0.00	0.00
Adverse events	-0.24	-1.14
Total	-1.14	-2.45

Is the company's modelling of carer disutility appropriate?

New analysis

Key issue: Mortality data and time horizon

Company change mortality data source and increase time horizon in the model in response to DG

Background

- The committee noted the median survival expected for people with DMD from the literature is around 30 years and was concerned that the natural history model may have overestimated life expectancy

Company response to DG

- Changed model to apply a per-cycle mortality risk
- Extrapolated published KM data from Broomfield et al. 2021 with a generalised gamma curve
- Mortality risk per-cycle set to highest risk from natural history data, the NHM, or Broomfield data
- Extended time horizon to 95 years to capture the small proportion of patients (15%) who are still alive at the end of the 50-year time horizon

NICE technical team comments and EAG critique

- The tail of the survival data still appears implausible
- However, without the capping (as modelled at ACM1) the survival probabilities show even less face validity
- With capping, the proportion surviving at 50 years for SoC was 18%, whereas without capping (as in ACM1) it was 23%
- The mortality capped data is the most plausible scenario available in the model – EAG used in its base case

Abbreviations: DG, draft guidance; DMD, Duchenne muscular dystrophy; EAG, external assessment group; KM, Kaplan-Meier; NHM, natural history model

New analysis

Key issue: Mortality data and time horizon

Company change mortality data source and increase time horizon in the model in response to DG

Proportion of patients alive by age in the company base case (run by NICE tech team)

Generalised gamma used

Extrapolations of Broomfield et al. 2021 KM data

Is the mortality data and time horizon used in the company's model suitable for decision-making?

NICE

Abbreviations: DG, draft guidance; KM, Kaplan-Meier

Company and EAG base case assumptions

All additional assumptions in company base case

Issue	Company base case	EAG base case
Treatment sequencing	Not included	Not possible to test in model.
Equal efficacy for vamorolone and corticosteroids	Equal efficacy	Reduced efficacy (20%)
Implementation of dose reduction	No change in efficacy for vamorolone after dose reduction, HR of [redacted] applied for transitions while SoC reduced dose is applied	No reduction in efficacy or AEs assumed for all treatments following dose reduction Hazard ratio assumption for no treatment arm set to base case (HR decreases through health states)
Uncertainty in long-term outcomes	Mild AEs set to 25% of the disutilities of moderate/severe AEs Behavioural issues disutility equal to severe side effects of anti-epileptic drugs (0.18)	Mild AEs set to 25% of the disutilities of moderate/severe AEs Behavioural issues QALY loss equal to moderate side effects of anti-epileptic drugs (0.09)
Stopping rule	Vamorolone stops at nighttime ventilation	No stopping rule
Source of health state costs	Landfeldt et al. 2017	BoI study
Patient utility estimates	Landfeldt et al. 2023	BoI study
Carer disutility estimates	2 carers for non-ambulatory health states, 0.16 base QALY loss for behavioural issues	1 carer, 0.16 QALY loss for behavioural issues applied only for 4–12-year-old boys
Mortality and time horizon	Highest of NHD, NHM, and Broomfield data for mortality, 95-year time horizon	Highest of NHD, NHM, and Broomfield data for mortality, 95-year time horizon

Cost effectiveness results summary

EAG corrections to company base case

- Corrected PSA and considered PSA incremental results
- Included total QALYs instead of just patient QALYs

The EAG corrected **company's** deterministic base case ICER for vamorolone compared with steroids is **below** £30,000/QALY

The **EAG's** deterministic base case ICER for vamorolone compared with steroids is significantly **above** £100,000/QALY

1.7x severity modifier was applied to patient QALYs in both base cases

Cost effectiveness results: Updated company base case

EAG corrections to company base case

- Corrected PSA and considered PSA incremental results
- Included total QALYs instead of just patient QALYs

Deterministic incremental **EAG corrected company** base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	incremental QALYs*	Fully incremental ICER (£/QALY)
Deflazacort	[redacted]	[redacted]	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Probabilistic incremental **EAG corrected company** base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	incremental QALYs*	Fully incremental ICER (£/QALY)
Deflazacort	[redacted]	[redacted]	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

*1.7 severity modifier applied

EAG results

Deterministic incremental results from corrected base case

	Scenario (applied individually to EAG corrected company base case)	Inc. costs	Inc. QALYs	ICER
	EAG corrected company base case	[redacted]	[redacted]	[redacted]
1	Reduced vamorolone efficacy (20%) for muscle function outcomes	[redacted]	[redacted]	[redacted]
2	No reduction in efficacy or AEs following dose reduction for all treatments	[redacted]	[redacted]	[redacted]
3	Health state utilities as per BOI study	[redacted]	[redacted]	[redacted]
4	Health state costs as per BOI study	[redacted]	[redacted]	[redacted]
5	Endocrinologist visit costs excluded for stunted growth	[redacted]	[redacted]	[redacted]
6	No stopping rule for vamorolone	[redacted]	[redacted]	[redacted]
7	Loss of ambulation due to non-vertebral fractures excluded	[redacted]	[redacted]	[redacted]
8	Number of carers per person: 1 for all health states	[redacted]	[redacted]	[redacted]
9	Behavioural issues disutility (0.06) applied for boys 4-12 years old	[redacted]	[redacted]	[redacted]
10	Spinal fusion surgery disutility duration (1 year)	[redacted]	[redacted]	[redacted]
11	**Cumulative EAG base case results**	[redacted]	[redacted]	[redacted]

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Note: Prednisone is the next best comparator for all individually applied scenarios; 1.7x severity modifier applied

Cost effectiveness results: Updated EAG base case

Deterministic incremental **EAG** base case results

Technology	Total costs (£)	Total QALYs*	Incremental costs (£)	Incremental QALYs*	Fully incremental ICER (£/QALY)
Deflazacort	[redacted]	[redacted]	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Probabilistic incremental **EAG** base case results

Technology	Total costs (£)	Total QALYs*	Incremental costs (£)	Incremental QALYs*	Fully incremental ICER (£/QALY)
Deflazacort	[redacted]	[redacted]	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The EAG ICERs for vamorolone compared with steroids are significantly above £100,000/QALY

*1.7 severity modifier applied

NICE

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

EAG exploratory analyses

EAG exploratory analyses individually applied to corrected company base case

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)	% change from EAG corrected company base case
EAG corrected company base case						
Deflazacort	[redacted]	[redacted]	-	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Reduced efficacy following dose reduction for all treatments (40% reduction applied for both vamorolone and SoC)						
Deflazacort	[redacted]	[redacted]	-	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC efficacy following dose reduction based on percentage reduction in efficacy following down-titration						
Deflazacort	[redacted]	[redacted]	-	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule applied to both vamorolone and SoC (while starting at night-time ventilation)						
Prednisone	[redacted]	[redacted]	-	-	-	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: 1.7x modifier applied to patient QALYs in all scenarios, all scenarios are deterministic

EAG exploratory analyses

EAG exploratory analyses individually applied to corrected company base case

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)	% change from EAG corrected company base case
EAG corrected company base case						
Deflazacort	[redacted]	[redacted]	-	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Mild AESI disutilities = 0.5* moderate/severe AESI disutilities						
Deflazacort	[redacted]	[redacted]	-	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utilities as per amended BOI study values						
Deflazacort	[redacted]	[redacted]	-	-	-	-
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

Note: 1.7x modifier applied to patient QALYs in all scenarios, all scenarios are deterministic

Other considerations

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Other considerations

Managed access

- The company have submitted a proposal for managed access

Uncaptured benefit

- Company highlight societal costs are key given the substantial burden faced by patients and carers
    - Caring for people with DMD is time-consuming and has a severe negative impact in several aspects of daily living including patients and parents' productivity
    - Economic analysis presented may miss key aspects of the disease which affects patients and their carers' lives

Abbreviations: DMD, Duchenne muscular dystrophy

Managed Access (1)

Vamolorone would be funded through the Innovative Medicines Fund (IMF), if recommended for managed access.

Committee can make a recommendation with managed access when:

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

Principle 2: The IMF should target the most promising medicines for which there is significant remaining uncertainty around the level of clinical benefit and cost-effectiveness. Medicines will be suitable if they address a high unmet need; provide significant clinical benefits; represent a step-change in medicine for patients and clinicians; and the new evidence to be generated is considered meaningful and could sufficiently reduce uncertainty.

Managed Access (2)

Company's Managed Access proposal

Uncertainties from the company:

- Long-term adverse events
- Efficacy of vamorolone after dose reductions
  - Effective dose range over the long term
  - Long term efficacy between 6 mg/kg and 4 mg/kg dosing

Data collection concerns:

- GUARDIAN study due to start [redacted] and run until [redacted]
- No RWE collected as part of MAA

Proposed data sources:

GUARDIAN study (sole data source):

- Open-label study [redacted]
- [redacted]
- Primary endpoint: [redacted]
- Proposes to collect comparative data through NorthStar programme to obtain a natural history data
  - Includes a natural history study, monitoring a group of more than 1,500 boys and young men with DMD over time. Data is collected at clinic appointments, then anonymised and shared upon request
- Evidence would be generated, but committee could not mandate what data is collected
- No guarantee on data quality, nor do the company have to provide the data collected outside of an MAA to the committee on exit

Abbreviations: DMD, Duchenne Muscular Dystrophy; RWE, Real World Evidence; MAA, Managed Access Agreement

Managed Access (3)

Managed Access Team identified uncertainties and further data collection

Key issues	Resolvable?	NICE managed access team comments
Efficacy of vamorolone and comparators after dose reductions	Medium	Only data on vamorolone can be collected through a period of managed access; comparative efficacy potentially difficult
Long term adverse events	Medium	GUARDIAN study has a treatment period of [redacted], which may not be sufficient to resolve uncertainty fully.
Equivalence vamorolone/prednisone	Unlikely	No comparative study planned
Vamorolone positioning	Unlikely	No RWE source; expert elicitation might be helpful
Modelling of stopping treatment	Unlikely	Modelling uncertainty / managed access would not help
Patient utility values	Unlikely	Modelling uncertainty / managed access would not help
Carer utility values	Unlikely	Modelling uncertainty / managed access would not help

Does vamorolone meet the criteria for managed access and align with the principles of the IMF (slide 30)? Would the proposed evidence collection resolve the uncertainties? Should data be collected in clinical practice as well as the GUARDIAN study?

*this is in addition to the treatment period in trials prior to entering GUARDIAN (4 to 7 years)

Summary

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Key issues for ACM2

Issue	ICER impact
Treatment sequencing	Unknown
Equal efficacy for vamorolone and corticosteroids	Unknown
Implementation of dose reduction	Large
Uncertainty in long-term adverse event outcomes	Unknown
Stopping rule [new evidence]	Large
Source of health state costs [new evidence]	Large
Patient utility estimates [new evidence]	Small
Carer disutility estimates [new evidence]	Small
Mortality and time horizon [new evidence]	Small

Other considerations
Managed access proposal
Equality considerations

Thank you.

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Supplementary appendix

Key issue: Source of health state cost data

New analysis

Company change source of health state cost data in response to DG

Health state	BoI study cost	Landfeldt et al. cost	Difference
Early ambulatory	£4,831	£12,623	£7,792
Late ambulatory	£2,726	£13,238	£10,512
Transfer	£3,133	£19,508	£16,375
HTMF, no ventilator	£1,872	£19,508	£17,636
No HTMF, no ventilator	£2,969	£32,639	£29,670
HTMF, night ventilator	£7,588	£37,513	£29,925
No HTMF, night vent	£7,171	£37,513	£30,342
Full time ventilation	£9,467	£43,050	£33,583

Health state costs from the project HERCULES BoI study and Landfeldt et al. 2017

Abbreviations: BOI, burden of illness; DG, draft guidance; HTMF, hand-to-mouth function

Company additional assumptions for ACM2

Assumption	Do EAG agree?
Mortality capping using Broomfield et al. 2021	Yes
Longer time horizon of 95 years	Yes
Health state costs based on Landfeldt et al. 2017	No
Growth stunting disutility increased to a duration of 8 years	Yes
Behavioural issues disutility increased to 18 months	Partially
Two caregivers assumed from loss of ambulation until death	No
Number of patients receiving spinal surgery is based on cumulative loss of ambulation and discontinuation	No
Patients may lose ambulation due to the occurrence of a long bone fracture	No
Bisphosphonates costs refined in line with Joseph et al. (2019) to reflect real-world clinical practice	Yes
Cataracts included with associated costs and disutilities (1 month disutility)	Yes
Average dose amended in line with average dose by age based on CINRG for prednisone and deflazacort	Yes
Hazard ratios applied to no treatment arm set to 2.41 for all health states	No
Include loss of ambulation due to fracture	No

What are committee's preferred assumptions?	Key question for committee	Impact
Treatment sequencing	Vamorolone use when CS unable to be used?	Unknown
Equal efficacy	Should a reduction in muscle function be modelled?	Small
Dose reduction	Company: HR of [redacted] for SoC? EAG: no reduction in efficacy/AEs for any treatments?	Large
Adverse events	**Behavioural issues:** Company: 0.18 disutility across all ages EAG: 0.09 disutility for ages 4-12 **Other issues:** Loss of ambulation due to non-vertebral fractures, spinal fusion surgery disutility length	Unknown
Stopping rule	Should a stopping rule be considered?	Large
Cost data	BoI study (EAG) or Landfeldt et al. 2017 (company)?	Large
Patient utility data	BoI study (EAG) or Landfeldt et al. 2023 (company)?	Small
Carer utility data	Should 2 carers be included in disutility modelling?	Large
Mortality and time horizon	Is a 95-year time horizon and updated mortality data appropriate?	Small
Preferred ICER	What is the committee's preferred ICER?	
Managed access	Is managed access suitable?	
Equality issue	Any further equality issues to consider?	

ACM 1 sides

Background on Duchenne muscular dystrophy

Genetic disorder which causes muscle weakness and progressive disability

Causes

- Genetic disorder caused by X-chromosome mutations in dystrophin gene, important for muscle function

Epidemiology

- Approx. 100 boys born each year with DMD and around 2500 people affected by DMD each year in the UK
- As mutation on X chromosome, almost exclusive prevalence of DMD in males

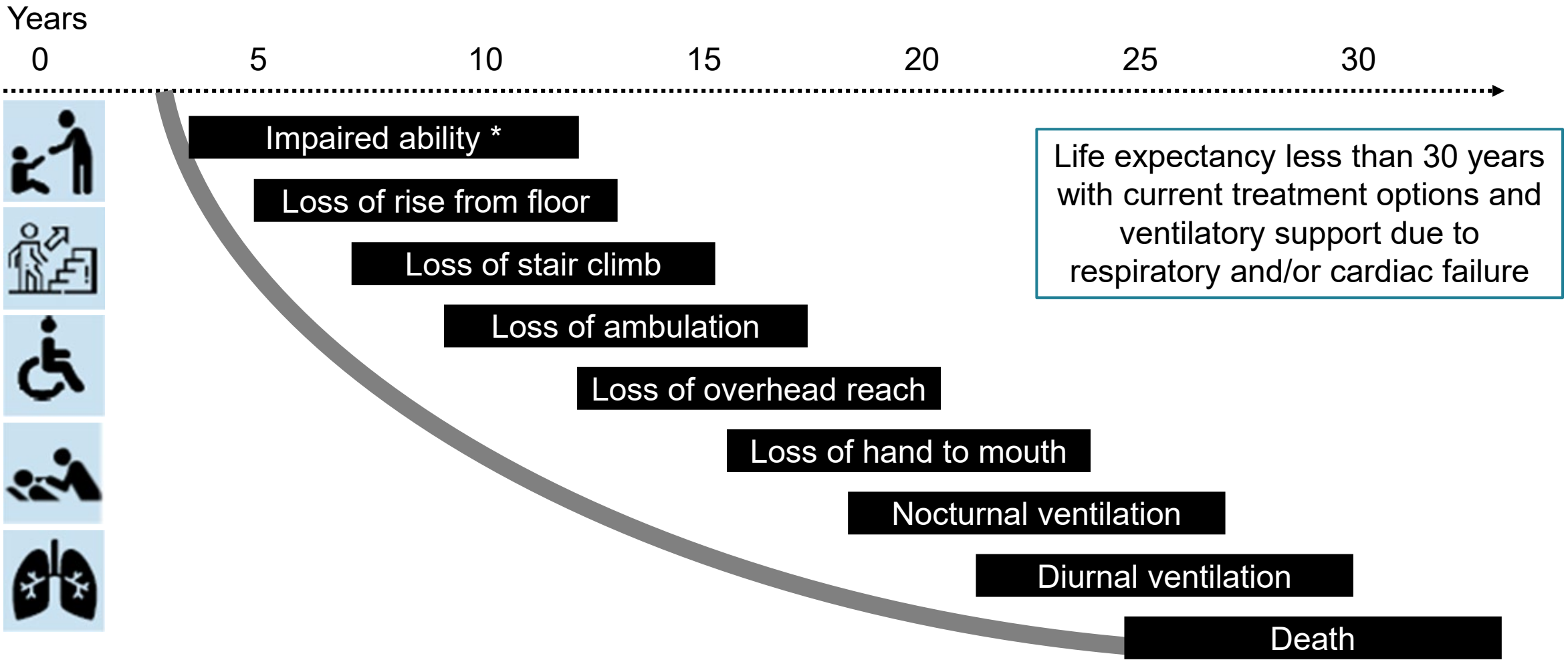
Symptoms and prognosis

- Age of onset usually 3–5 years old; but symptoms sometimes as young as 2 years old
- Early signs include large calf muscles, delay to sit and stand, Gower's movement and unusual gait
    - Increased difficulty when mobilising, and may have behavioural or learning difficulties
- Young adults need help with self-care activities
- Respiratory and cardiac function weaken progressively, leading to assisted ventilation and cardiac failure
- Life expectancy of people with DMD depends how quickly and intensely muscle weakness progresses
    - Average lifespan less than 30 years due to respiratory and/or cardiac failure

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

Natural disease course – stylised

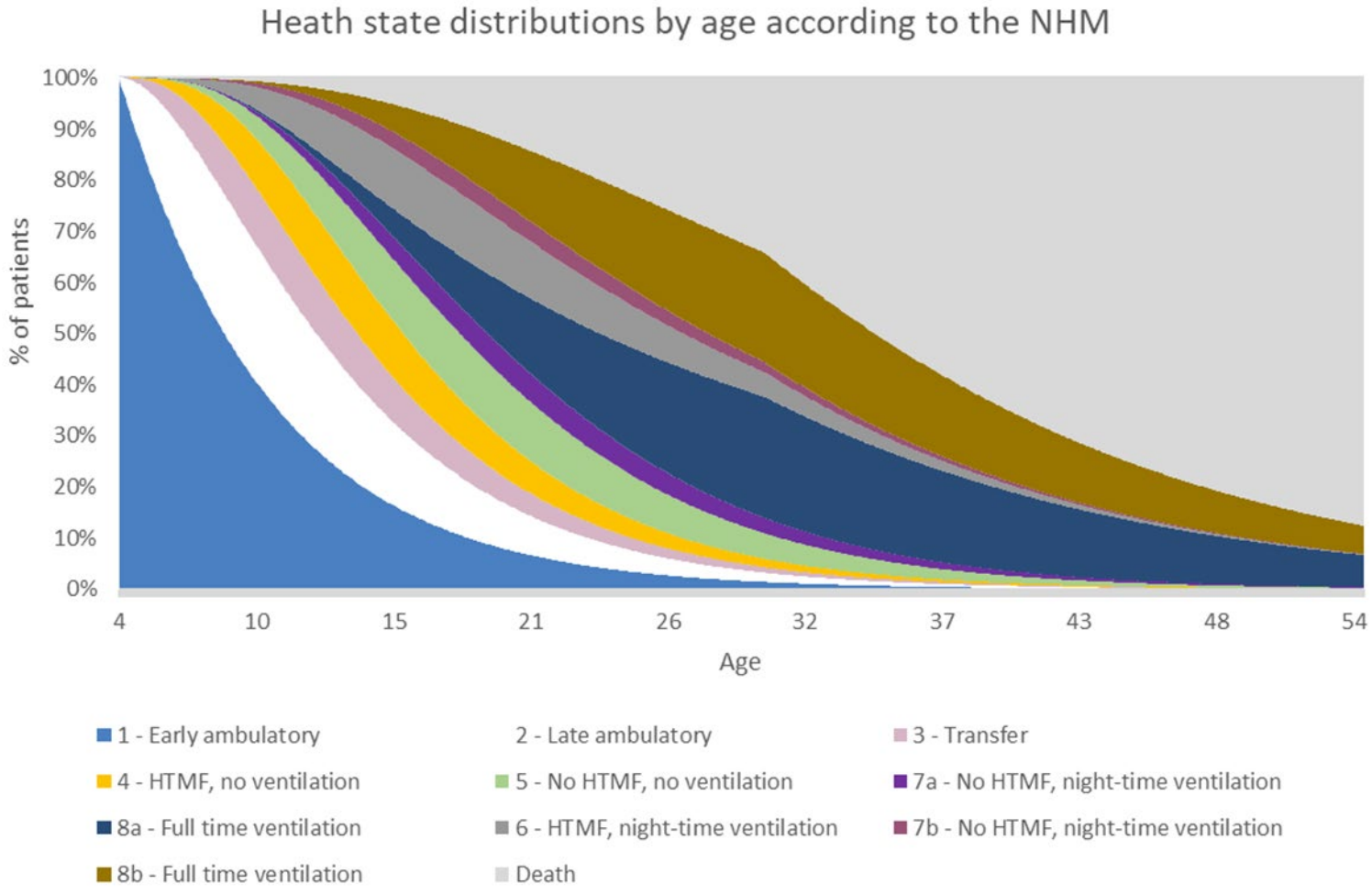
Typical muscle degeneration seen in people with Duchenne muscular dystrophy



Notes: * impaired ability to hop, run, jump, rise from floor.

Natural disease course – modelled

Natural history model developed from Project HERCULES informs baseline risk



Background

- Project HERCULES is UK-led project initiated by Duchenne UK to develop tools and evidence to support HTA for new DMD treatments
- Cost-effectiveness model conducted using Project HERCULES framework
- Natural history transitions used as backbone of the model for all treatments
  - Primary data was D-RSC database
- Increased mortality rate applied at 30 years, approximately corresponding to median survival

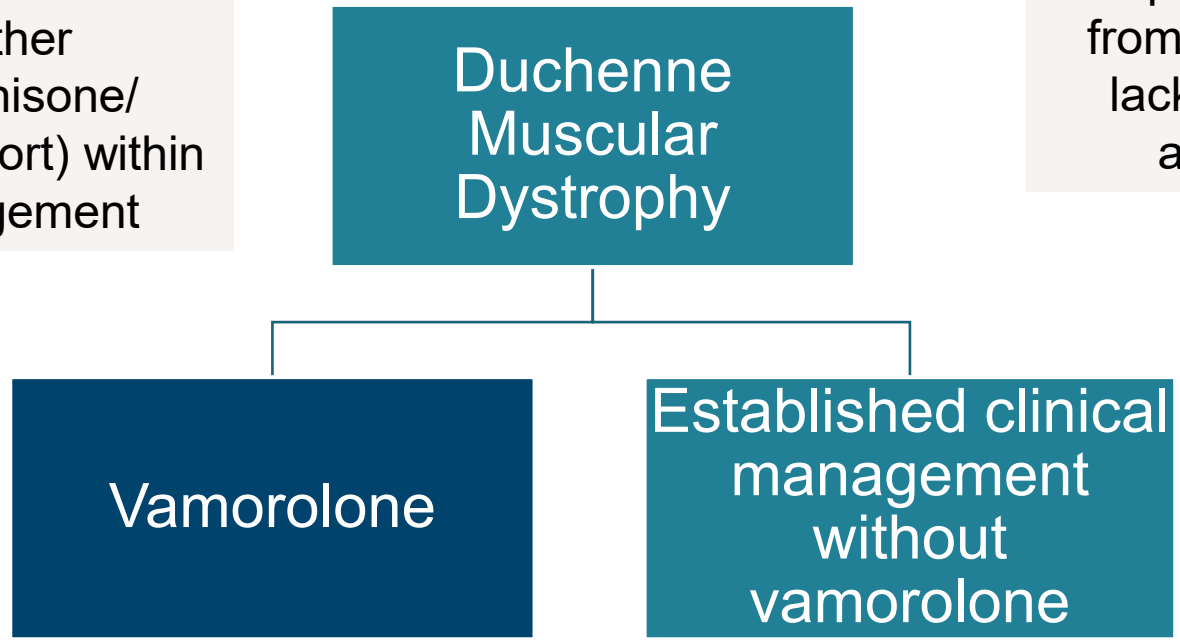
Does the natural history model reflect clinical outcomes for people with DMD in the UK?

Abbreviations: DMD, Duchenne muscular dystrophy; D-RSC, Duchenne Regulatory Science Consortium; FVC, forced vital capacity; HTA, health technology assessment; HTMF, hand-to-mouth function; NHM, natural history model; UK, United Kingdom.

Treatment pathway

Company position vamorolone as alternative to other glucocorticoids

Company positions vamorolone as an alternative to other glucocorticoids (prednisone/ prednisolone or deflazacort) within current clinical management



Company suggest vamorolone differs from traditional glucocorticoids by lack of hydroxy-carbonyl group; alters structure and activity

- Is it appropriate to compare vamorolone to prednisone/prednisolone or deflazacort?
- How are steroid used in practice? Is prednisone or deflazacort preferred for initial treatment? Do people switch treatments?
- How would vamorolone be used in practice? Treatment naïve or those who can't tolerate?

Abbreviations: DMD, Duchenne muscular dystrophy.

Patient perspectives

The condition is associated with significant impact on patients and carers

Submissions from Action Duchenne, Muscular Dystrophy UK and Duchenne UK

- Devastating diagnosis. Substantial disease-related burden for patients and caregivers in terms of physical, logistical, emotional, psychological, and financial burdens
- As DMD progresses, children experience decline in independent walking, strength and mobility in arms, ability to feed themselves, or undertake self-care activities
- Most experience serious respiratory, orthopaedic, and cardiac complications. By 18, majority require ventilation support at night
    - Respiratory complications and cardiomyopathy common causes of death
- MD UK Survey Feb. 2024: 100% of respondents reported disadvantages for corticosteroid treatment currently available through the NHS
    - 5 main ones: weight gain; negative behaviour changes; growth restriction; reduced bone density; and delayed puberty
    - limited choice of two steroids both with distinctive disadvantages. Unmet need for an option with good safety profile

"vamorolone didn't delay growth at all… able to walk until later age…great advantage of vamorolone…when comparing the two treatments [our 2 sons received]"

"Most cared for on a day-to-day, long-term basis by a combination of informal caregivers, family members and formal caregivers"

NICE

Abbreviations: DMD, Duchenne muscular dystrophy; MD, muscular dystrophy; NHS, National Health Service; UK, United Kingdom.

Clinical perspectives

Vamorolone an alternative to currently available steroids

Submissions from the BSPED, BPABG, and ABN

- Primary symptoms caused by lack of dystrophin in the muscle. Children lose ability to walk independently and most need wheelchairs between 8 and 13
- Currently use steroids associated with significant side effects – proportion unable to tolerate steroids so need alternatives
- Vamorolone treatment "dissociates efficacy from safety" and aims to:
    1. Maintain muscle strength and function
    2. Improve height velocity in children with DMD
    3. Possible cardioprotective effect
    4. Protect bones
- Anticipated use primarily for patients who cannot tolerate current corticosteroids
- Might improve some aspects of quality of life, related to fewer adverse effects and better adherence

"Currently patients have limited treatment options, that effectively delay or reverse disease progression"

"Expect it to deliver similar benefits as current treatment but with better tolerability and adherence"

NICE **Abbreviations:** ABN, Associate of British Neurologists; BSPED, British Society for Paediatric Endocrinology & Diabetes; BPABG, British Paediatric And Adolescent Bone Group; DMD, Duchenne muscular dystrophy; UK, United Kingdom.

Equality considerations

NICE kept remit and population broad to be inclusive to all

- Vamorolone has been studied in clinical trials in boys aged 4 years and older
- Scoping consultation noted that corticosteroids are not routinely used or recommended in female carriers, even if symptomatic
- Many DMD patients have significant mobility issues
    - Concerns about travel distance to receive treatment given the level of disability many patients have should be considered, so no patients are denied access to a treatment due to travel requirements

Are there any potential equality issues that the committee should consider?

Abbreviations: DMD, Duchenne muscular dystrophy.

Vamorolone (Agamree, Santhera)

Technology details

Marketing authorisation	Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older MHRA granted Jan 2024
Mechanism of action	Differs from traditional glucocorticoids by its lack of an 11β hydroxy-carbonyl group, which alters structure and activity: 1. High affinity to glucocorticoid receptor with suppression of pro-inflammatory pathways 2. High affinity to mineralocorticoid receptor, potentially benefiting heart function 3. Membrane stabilisation and promotion of membrane repair
Administration	In people less than 40 kg, 6.0 mg/kg/day orally In people 40 kg and above, 240 mg (equivalent to 6 ml) once daily orally Daily dose may be reduced to 4 mg/kg/day, or 2 mg/kg/day based on individual tolerability

Price	• 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
	  • Vamorolone has a confidential commercial arrangement (simple PAS)

Abbreviations: kg, kilogram; mg, milligram; MHRA, Medicines and Healthcare products Regulatory Agency; ml, millilitre; PAS, patient access scheme; UK, United Kingdom.

Key issues

Issue	ICER impact
Clinical effectiveness issues	
Equal efficacy for vamorolone and corticosteroids	Unknown
Treatment sequencing	Unknown
Cost-effectiveness issues	
Uncertainty about long-term discontinuation rates for vamorolone	Large
Inconsistent assumptions for vamorolone and SoC following dose reduction	Moderate
Uncertainty over long-term growth and behavioural outcomes following vamorolone	Moderate
Face validity of patient and carer utility estimates	Unknown
Severity modifier (1.7x vs 1.2x modifier)	Large
Additional cost-effectiveness issues detailed in back up	
Use of blended comparator creates uncertainty	Moderate
Non-reference case health state costs	Small

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Abbreviations: SoC, standard of care.

Clinical effectiveness

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Key clinical trials

Vamorolone was investigated in VISION-DMD

Clinical trial designs and outcomes

	VISION-DMD	VBP15-002/VBP15-003/VBP15-LTE
Design	Phase IIb, double-blind, randomised, placebo and active-controlled trial	Phase IIa, open-label trial of vamorolone with sequential multiple ascending doses
Population	Treatment-naïve boys with DMD aged 4-7	Boys aged 4 to <7 years with DMD
Intervention	Vamorolone 6.0 mg/kg/day or 2.0 mg/kg/day	Vamorolone 0.25 mg/kg/day or 0.75 mg/kg/day or 2.0 mg/kg/day or 6.0 mg/kg/day
Comparator(s)	Prednisone 0.75 mg/kg/day or placebo	Not applicable
Duration	24 weeks comparative; plus 24 weeks ext.	VBP15-002: 2 weeks then 2-week washout
Primary outcome	TTSTAND	Safety and pharmacokinetics
Key secondary outcomes	6MWT; TTRW; TTCLIMB; NSAA score; Knee extension and elbow flexor muscle strength; HRQL; Safety	TTSTAND; 6MWT; TTRW; TTCLIMB; NSAA
Locations	US, Canada, Israel and Europe, incl. UK	Canada, US, UK, Australia, Sweden, Israel
Used in model?	Yes	Yes

Abbreviations: 6MWT, six-minute walking test; DMD, Duchenne muscular dystrophy; ext., extension; kg, kilogram; mg, milligram; NSAA, North Star Ambulatory Assessment; TTCLIMB, time to climb; TTRW, time to run/walk 10 meters; TTSTAND, time to stand; UK, United Kingdom; US, United States.

VISION-DMD results – muscle function (1)

Vamorolone muscle efficacy outcomes numerically lower than prednisone, not statistically significant; EAG suggest potentially meaningful impacts for patients

EAG comments

- VISION-DMD results showed people receiving vamorolone or prednisone had a clinically meaningful improvement in muscle function outcomes compared to placebo after 24 weeks
- However, vamorolone did not out-perform prednisone in muscle function; EAG argue these trends could lead to meaningfully poorer outcomes for vamorolone compared with prednisone after 24 weeks
- Vamorolone efficacy stabilised after 24 weeks, but no comparator prednisone arm beyond 24 weeks

VISION-DMD efficacy results (24 weeks) – key muscle function outcomes

	TTSTAND velocity, rises/sec		6MWT distance, metres	
	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	0.22 (0.06)	0.19 (0.06)	343.3 (55.84)	312.5 (56.19)
Week 24, mean (SD)	0.29 (0.09)	0.24 (0.08)	395.5 (57.32)	355.9 (50.92)
CFB at Week 24, mean (SD)	0.07 (0.07)	0.05 (0.07)	39.7 (30.620	28.8 (49.66)
LSM (SE) change from baseline	0.07 (0.01)	0.05 (0.01)	48.23 (9.12)	28.34 (9.56)
LSM difference (SE) vs prednisone	NA	-0.02 (0.02)	NA	-19.89 (13.10)
95% CI vs prednisone	NA	-0.06, 0.02	NA	-45.93, 6.15
p-value vs prednisone	NA	0.2976	NA	0.1326

Note: Larger CFB numbers show higher muscle function/improvement; positive LSM numbers show vamorolone improves more than prednisone

Abbreviations: 6MWT, six-minute walking test; CFB, change from baseline; DMD, Duchenne muscular dystrophy; EAG, external assessment group; kg, kilogram; LSM, least squares mean; mg, milligram; n, number; NA, not applicable; SD, standard deviation; SE, standard error; TTSTAND, time to stand.

VISION-DMD results – muscle function (2)

Vamorolone muscle efficacy outcomes numerically lower than prednisone, not statistically significant, but could translate into meaningful impacts for patients

EAG comments

- EAG consider it likely that vamorolone would not be as effective as prednisone in slowing down disease progression in muscle function despite the lack of statistical significance at 24 weeks
  - May be due to small sample sizes and variability in treatment outcomes for participants
- Further comparative evidence between vamorolone and prednisone (or deflazacort) at later timepoints would be useful to determine the extent of differences in muscle function outcomes

VISION-DMD comparative efficacy results (24 weeks) – all muscle function outcomes

	LSM difference (SE) vs prednisone	95% CI vs prednisone	p-value vs prednisone
TTSTAND velocity change from baseline, rises/sec	-0.02 (0.02)	-0.06, 0.02	0.2976
6MWT distance change from baseline, metres	-19.89 (13.10)	-45.93, 6.15	0.1326
TTRW velocity change from baseline, metres/sec	-0.11 (0.08)	-0.26, 0.04	0.1381
TTCLIMB velocity change from baseline, step/sec	-0.05 (0.02)	-0.09, -0.01	0.0193
NSAA score change from baseline	-1.44 (0.83)	-3.09, 0.20	0.0848
Knee extension muscle strength change from baseline	-0.91 (0.48)	-1.87, 0.05	0.0617

Note: Positive LSM numbers show vamorolone improves outcomes more than prednisone; negative numbers show vamorolone improves outcomes less than prednisone

Abbreviations: 6MWT, six-minute walking test; CI, confidence interval; cm, centimetre; EAG, external assessment group; kg, kilogram; mg, milligram; n, number; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SE, standard error; TTCLIMB, time to climb; TTRW, time to run/walk 10 metres; TTSTAND, time to stand.

VISION-DMD results – safety

People on vamorolone had less moderate to severe TEAEs than prednisone in VISION-DMD

Company

- Number experiencing TEAEs similar across arms
- No meaningful differences after 24 weeks
- Increased risk of behavioural problems with prednisone but severity unclear
- Increased risk of weight gain following vamorolone compared to prednisone, though rates small
- No evidence of growth stunting with vamorolone

EAG comments

- Main potential benefit may be reduced incidence of specific AEs, such as stunted growth, behavioural issues and bone health
- Short follow-up and uncertain due to low events, but data promising; suggest risks lower with vamorolone
- May be preferred based on safety profile, despite risk not as effective in maintaining muscle function

VISION-DMD safety – TEAEs

TEAEs	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)
TEAEs (%)	26 (83.9)	25 (89.3)
Drug-related TEAEs (%)	14 (45.2)	19 (67.9)
Severe TEAEs (%)	1 (3.2)	0

Moderate to severe AESI rates by treatment in VISION-DMD

Treatment	Prednisone	Vamorolone
Weight gain	3.23%	0.00%
Behavioural issues	25.81%	0.00%
Cushingoid effects	0.00%	3.57%
Immune suppressed/infection	12.90%	0.00%
GI symptoms	3.23%	0.00%
Diabetes	0.00%	0.00%
Skin/Hair change	3.23%	0.00%

Note: Company only included moderate to severe events, excluding less severe events resulted in a substantially lower incidence compared with trial data

NICE

Abbreviations: DMD, Duchenne muscular dystrophy; kg, kilogram; mg, milligram; TEAE, treatment emergent adverse event.

Key issue: Equal efficacy for vamorolone and corticosteroids

EAG suggest numerical differences important; disagree with equal efficacy assumption

Background

- Vamorolone was compared to another corticosteroid (prednisolone) in VISION-DMD

Company

- Suggest vamorolone 6.0 mg/kg/day showed comparable efficacy to prednisone in VISION-DMD
- Conclusion of equivalence from VISION-DMD data used to drive efficacy economic model

EAG comments

- Disagree with interpretation; explain prednisone offered benefit over vamorolone at 24 weeks for outcomes related to muscle function; which when extrapolated, are likely clinically meaningful for people with DMD
- Consider prednisone more effective than vamorolone and assumption of equivalence inappropriate
- Vamorolone may still be a valued treatment option despite the potential poorer muscle function outcomes due to alternative safety profile
- Model doesn't capture potential clinical difference, so EAG unable to address this during this appraisal

Other considerations – Associate of British Neurologists

- Vamorolone causes fewer and less-severe side effects without compromising anti-inflammatory properties
- We would expect it to deliver similar benefits as current treatment but with better tolerability and compliance

Could vamorolone and SoC be considered to have equal efficacy?

NICE

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, external assessment group; kg, kilogram; mg, milligram.

Key issue: Treatment sequencing

Evidence based on treatment-naïve population and no sequencing

Background

- Initial therapy (prednisone/prednisolone or deflazacort) for DMD is largely based on parent preferences
- In clinical practice, treatment may be switched due to efficacy or adverse events

Company

- VISION-DMD included treatment-naive people with DMD, and vamorolone positioned as an alternative to initial treatment with other current corticosteroid treatments

EAG comments

- Children may change steroid treatment due to efficacy and adverse effects, but sequencing not included
- Plausible that vamorolone would be received at varying lines of treatment depending on parent preferences
- Trial based on a treatment-naïve population; would effect of vamorolone vary according to its positioning?
- Economic model not structured to allow people to have a sequence of glucocorticoid treatments for DMD

Other considerations – ABN, Muscular Dystrophy UK and Action Duchenne

- Likely used in patients who could not tolerate corticosteroids due to side effects or with poor adherence
- Those forced to withdraw from steroid treatment despite advantages and would benefit from an alternative

Should the modelling account for treatment switching/sequencing? Is VISION-DMD evidence generalisable to previously treated people?

NICE

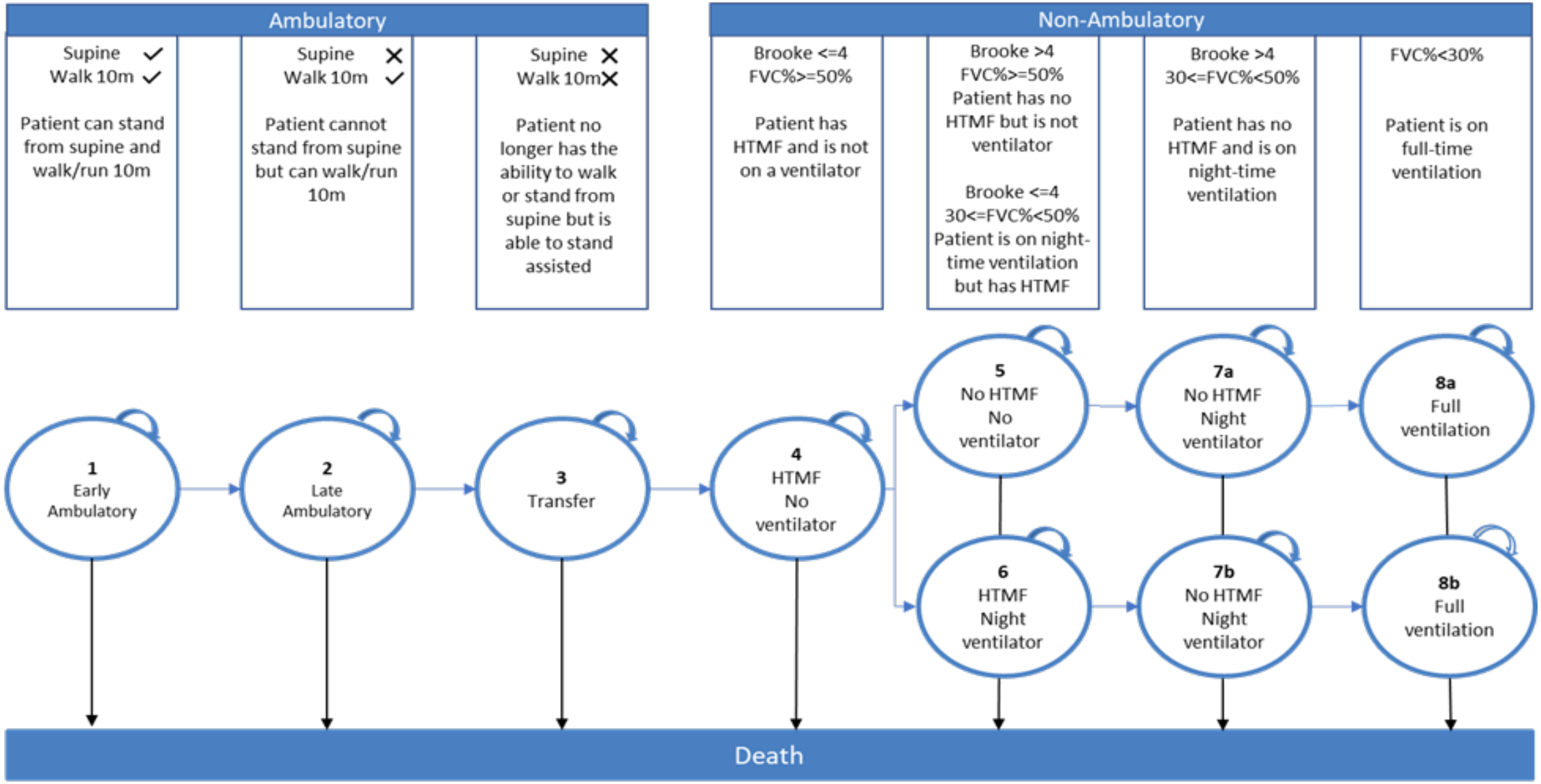
Abbreviations: ABM, Associate of British Neurologists; DMD, Duchenne muscular dystrophy; EAG, external assessment group; UK, United Kingdom.

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Markov model with 8 health states before death based on project HERCULES



Abbreviations: DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; HTMF, hand-to-mouth function.

How company incorporated evidence into model

Company use HERCULES natural history data to drive model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	Starting age: 4.1 years, based on UK study by Vry et al. Scenario: 5 years
Time horizon, discounting	50 years, 3.5%
Intervention efficacy	Vamorolone, informed by HERCULES natural history (equivalent to SoC)
Comparator efficacy	SoC (prednisolone and deflazacort), informed by HERCULES natural history
Adverse events	AEs of special interest and acute events from **VISION-DMD**, sum of treatment specific + no treatment events applied in model; impacts patient and carer QoL
Discontinuation	Informed by **VISION-DMD** for vamorolone and CINRG for SoC
Utilities	Patient utility from BOI study (Noble-Longster et al. 2022), disease specific DMD-QoL; Carer disutility from a blend of Landfeldt et al. (2017) and BOI study
Resource use and costs	SoC costs from BNF; Health state costs informed by HERCULES; AE unit costs from standard sources

Abbreviations: AE, adverse event; BNF, British National Formulary; BOI, burden of illness; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; QoL, quality of life; SoC, standard of care; UK, United Kingdom.

Key issue: Long-term discontinuation rates

Assumptions around discontinuation rates have large impact on the ICER

Background

- Availability and maturity of treatment discontinuation data varied (1 year vamorolone vs 14 years SoC)
- Greater time on vamorolone results in more QALYs and much more costs

Company

- 28/30 (93.3%) of vamorolone and 30/31 (96.8%) of prednisone arm completed VISION-DMD to week 24
- VISION-DMD for vamorolone and CINRG data for SoC extrapolated with log-logistic models
- People who discontinue vamorolone or SoC receive 'no treatment' efficacy/safety assumptions

EAG and technical team comments

- Company's extrapolation of short-term data provided advantage for vamorolone, potentially not justified
  - Unrealistic to model less time on treatment compared with SoC given proposed safety differential?
  - Predicts mean time on treatment of [redacted] years for vamorolone versus average of [redacted] years for SoC
- EAG base case assumes proportion discontinuing vamorolone is equal to the same as long term deflazacort CINRG data (as deflazacort KM resembled better adherence expected given side effect claim)
- Considered Gen gamma to be best fitting curve for SoC, which applied to vamorolone as well in base case

Other considerations – Action Duchenne

- Patient groups expect vamorolone may provide benefits of corticosteroids, with a reduction in side effects

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; EAG, external assessment group; Gen, generalised; KM, Kaplan–Meier; SoC, standard of care; TT, technical team.

Long-term discontinuation

Long-term discontinuation uncertain, alternative assumptions have large impact on cost effectiveness

Company treatment discontinuation extrapolations

Company extrapolate short-term VISION-DMD data for vamorolone

EAG treatment discontinuation assumptions

EAG assume vamorolone time on treatment similar to long-term deflazacort data and use GenGamma model

How should discontinuation of vamorolone be modelled?

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, external assessment group; KM, Kaplan–Meier.

Return to ACM 2 slide

Key issue: Dose reduction

SoC dose reduction impacts costs and benefits; vamorolone impacts only costs

Background

- People in the model start on optimal dosing for both treatment arms but may dose-reduce or discontinue
- Dose reductions based on VISION-DMD (vamorolone) and Birnkrant et al. (SoC), but application of modelled dose reduction differs between treatment arms

Company

- Down-titration for SoC calculated from CINRG data, applied proportionally reduced transition probabilities
- Down-titration for vamorolone was not part of the VISION-DMD protocol, but model does account for dose reduction at a constant rate between Month 3 and 6; vamorolone dose reduction only impacts costs

EAG comments

- Consider asymmetry between reduced transition probabilities for SoC patients but not vamorolone inappropriate; overestimates QALY gain from vamorolone whilst reducing cost
- 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
  - Reduces QALY gain, increases ICER; increases SoC outcomes, impacts severity
- In reality, EAG expect a reduction in efficacy following down-titration, but not possible in current model

How should dose reductions for vamorolone be modelled?

NICE

Abbreviations: DMD, Duchenne muscular dystrophy; EAG, external assessment group; QALY, quality-adjusted life-year; SoC, standard of care.

Key issue: Uncertainty in long-term outcomes

Company extrapolate short-term safety outcomes from limited data

Background

- Stunted growth and behavioural issues are known side effects of existing SoC for DMD
- Large proportion of vamorolone incremental QALY gains come from estimated reduction in adverse events
- Behavioural issues only event with an AE utility decrement for carers so drives almost all carer QALYs gains

Company

- 72% of SoC arm experience stunted growth (based on 6-year case-series follow-up) versus 0% of vamorolone arm (based on 24-week VISION-DMD)
- 5% of SoC arm modelled to have monthly behavioural issues versus 0% of vamorolone arm
- Other adverse events have differential rates between vamorolone and SoC (back up slide)

EAG and technical team comments

- General uncertainty in vamorolone assumptions, given they are based on short-term follow-up
- Majority of QALY gains in the model for vamorolone come from a reduction of AEs compared to SoC
  - Virtually all carer QALY gain from behavioural AE
- EAG base case assumes small vamorolone proportion experience stunted growth and behavioural issues
  - Changes lead to moderate increase in ICER due to increased cost and disutility associated with events

What is the appropriate approach modelling long-term adverse event outcomes?

Abbreviations: AESI, adverse event of special interest; DMD, Duchenne muscular dystrophy; EAG, external assessment group; SoC, standard of care.

Health-related quality of life – patient

ACM2 utility slide

QALYs driven by reducing number of AEs and time spent in early ambulatory state

Company

- Health state utility calculates using disease specific DMD-QoL; Further utility decrements applied for adverse/acute events
- Utility and disutility values applied consistently across arms, but AE rates differed by arms

EAG and technical team comments

- EAG considered the magnitude of utility decrements to be broadly reasonable
- Vamorolone affects QALYs by reducing number of AEs
- EAG less concerned with utility values as applied consistently across arms, but extrapolation of outcomes impacts overall QALY difference

Health state utility values and disaggregated QALYs

Ambulatory class	Utility	Vamorone QALYs	SoC QALYs	Diff.
Early ambulatory	0.70	2.55	2.33	0.22
Late ambulatory	0.49	1.09	1.09	
Transfer	0.38	0.36	0.36	
HTMF, no ventilation	0.54	0.61	0.62	-0.01
No HTMF, no ventilation	0.51	0.67	0.68	-0.01
HTMF, night-time ventilation	0.53	0.67	0.68	-0.01
No HTMF, night-time ventilation	0.52	0.51	0.52	-0.01
Full-time ventilation	0.33	1.69	1.72	-0.03
Total health state QALYs		**8.15**	**8.01**	**0.14**
Adverse events		-0.15	-1.08	0.93
Acute events		-0.01	-0.02	0.01
Carer QALYs *		-0.81	-1.31	0.50
Total QALYs		**7.18**	**5.60**	**1.58**

* Carer QALYs discussed on next slide

Do utility values and impact of adverse events have face validity?

Abbreviations: AE, adverse event; DMD, Duchenne muscular dystrophy; EAG, external assessment group; HRQoL, health-related quality of life; HTMF, hand-to-mouth function; QALY, quality-adjusted life-year; SoC, standard of care.

Health-related quality of life – carer

Carer QALYs driven by extrapolated rates of behavioural issues

Company

- Base case used a blend of Landfeldt and BOI studies for carer health state disutilities
- Further AE disutility applied for boys experiencing behavioural issues (from epilepsy study)
  - 5% of SoC versus 0% of vamorolone arm
  - Note in model both arms apply no treatment events as well as treatment specific
- No utility impact applied for other AEs

EAG and technical team comments

- Disutilities applied consistently to both sides of model
- Carer quality of life makes up ~30% of incremental QALYs
  - Driven by behavioural issues adverse event

Is the approach for carer quality of life appropriate?

Carer utility loss as progress through health states

Ambulatory class	Carer disutility
Early ambulatory	0
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

Carer QALY loss due to adverse/acute events

Adverse events	QALY loss per event
Behavioural issues	-0.06

Disaggregated carer QALYs

	Vamorolone	SoC
Sum of health states	-0.77	-0.76
Acute events	0.00	0.00
Adverse events	-0.05	-0.54
Total	-0.81	-1.31

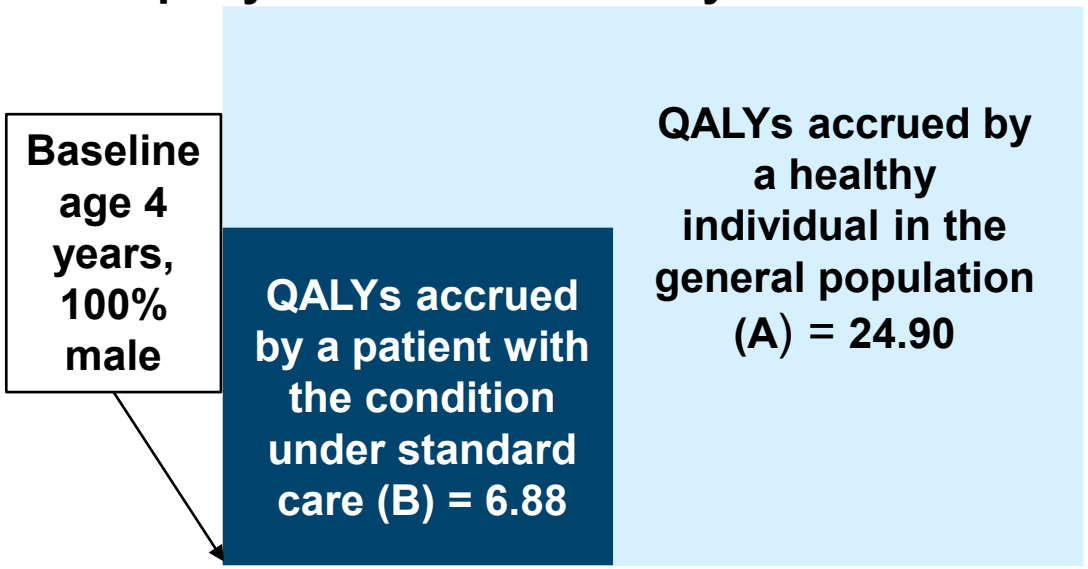
Abbreviations: AE, adverse event; BOI, burden of illness; EAG, external assessment group; HTMF, hand-to-mouth function; QALY, quality-adjusted life-year; SoC, standard of care.

QALY weighting for severity

QALY weightings applied to patient QALYs only; calculations sensitive to starting age

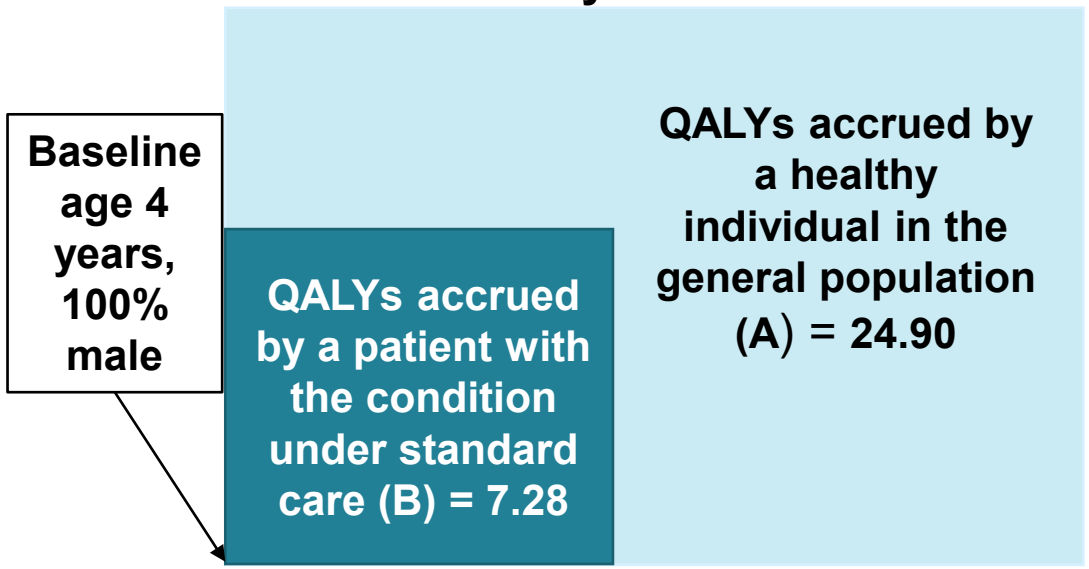
Note: VISION-DMD SoC mean age 5.54

Company estimate of severity



Absolute shortfall =
24.90 – 6.88 = **18.02** (x1.7)
Proportional shortfall =
(24.90 – 6.88) / 24.90 = **72.37%** (x1.2)

EAG estimate of severity



Absolute shortfall =
24.90 – 7.28 = **17.62** (x1.2)
Proportional shortfall =
(24.90 – 7.28) / 24.90 = **70.77%** (x1.2)

Should a severity weighting be applied? If so, which weight?

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.

Other key issues

Model has other outstanding uncertainties that impact cost effectiveness

Use of blended comparator creates uncertainty

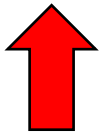
- Primary comparator in base case was SoC, assumed to be 85% prednisone and 15% deflazacort
- EAG concerned pooling evades relevant comparisons along the efficacy frontier
- Prednisone and deflazacort have distinct efficacy/safety profiles, differences between costs and outcomes
- EAG compared to each separately in fully incremental analysis; applied 50/50 split in scenario

Non-reference case health state costs

- NICE reference case specifies costs should be of NHS and personal social services perspective only
- Company included additional costs such as patient out of pocket costs (OTC medications, transport and alternative and complementary therapies) and transfer payments (described as direct non-medical costs)
- EAG excluded out-of-scope costs, to limit the perspective to the NICE reference case

Abbreviations: NHS, National Health Service; OTC, over the counter; QALY, quality-adjusted life-year; SoC, standard of care.

Differences in company and EAG base case assumptions

Assumption	Company base case	EAG base case	Impact
Comparators	Blended SoC comparator	Prednisone/deflazacort considered individually	
LT outcomes	Vamorolone stunted growth and behavioural issues rates, 0%	Vamorolone stunted growth and behavioural issues rates, 5%	
Dose reduction	Vamorolone remains at full efficacy SoC reduced efficacy	SoC on reduced dose remain at full efficacy to match vamorolone assumption Scenario investigates impact of reduction on SoC treatment effect and AE exposure	
Treatment discontinuation	Short-term VISION-DMD data (48 weeks) extrapolated	Rates assumed same as deflazacort, based on long-term CINRG data (~14 years)	
Costs	Non-reference health state and spinal fusion surgery cost items included; growth hormone costs included	Non-reference health state and spinal fusion surgery cost items excluded; growth hormone costs excluded	
Severity	x1.7 modifier used	x1.2 modifier used	

Which assumptions do the committee prefer?

Abbreviations: AE, adverse event; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; EAG, external assessment group; SoC, standard of care.

Cost effectiveness results: EAG corrected company base case

Full cost-effectiveness results containing confidential discounts are presented in Part 2

EAG corrections to company base case

- Considered incremental results
- Company applied severity modifier to both patient and carer QALYs; EAG applied to patient QALYs only
- Corrected an error in probabilistic analysis to allow PSA to run with generalised gamma survival model
- Fixed error in patient utility values (no impact in results)

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Prednisone	[redacted]	10.567			
Deflazacort	[redacted]	10.657	[redacted]	0.089	[redacted]
Vamorolone	[redacted]	12.771	[redacted]	2.204	[redacted]

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Prednisone	[redacted]	10.682			
Deflazacort	[redacted]	10.918	[redacted]	0.236	[redacted]
Vamorolone	[redacted]	13.019	[redacted]	2.337	[redacted]

Cost effectiveness results: EAG base case

Deterministic incremental results from corrected base case

	Scenario (applied individually to EAG corrected company base case)	Next best comparator	Inc. costs	Inc. QALYs	ICER
	EAG corrected company base case	Prednisone	[redacted]	2.204	[redacted]
1	Symmetric impact of down-titration of treatment dose	Prednisone	[redacted]	1.508	[redacted]
2	5% stunted growth and behavioural issues with vamorolone in long-term	Prednisone	[redacted]	2.132	[redacted]
3	Treatment discontinuation extrapolated using gen-gamma with vamorolone discontinuation assumed same as deflazacort CINRG	Prednisone	[redacted]	3.115	[redacted]
4	Exclude out-of-scope costs	Prednisone	[redacted]	2.204	[redacted]
5	Exclude growth hormone costs	Deflazacort	[redacted]	2.115	[redacted]
6	1.2x QALY multiplier applied	Prednisone	[redacted]	1.703	[redacted]
7	**Cumulative EAG base case results**	Deflazacort	[redacted]	1.545	[redacted]

Other considerations

Managed access

- No managed access proposal has been made.

Uncaptured benefit

- Company highlight societal costs are key given the substantial burden faced by patients and carers
    - Caring for people with DMD is time-consuming and has a severe negative impact in several aspects of daily living including patients and parents' productivity
    - Economic analysis presented may miss key aspects of the disease which affects patients and their carers' lives

Key issues

Issue	ICER impact
Clinical effectiveness issues	
Equal efficacy for vamorolone and corticosteroids	Unknown
Treatment sequencing	Unknown
Cost-effectiveness issues	
Uncertainty about long-term discontinuation rates for vamorolone	Large
Inconsistent assumptions for vamorolone and SoC following dose reduction	Moderate
Uncertainty over long-term growth and behavioural outcomes following vamorolone	Moderate
Face validity of patient and carer utility estimates	Unknown
Severity modifier (1.7x vs 1.2x modifier)	Large
Additional cost-effectiveness issues detailed in back up	
Use of blended comparator creates uncertainty	Moderate
Non-reference case health state costs	Small

NICE

Abbreviations: SoC, standard of care.

NICE National Institute for Health and Care Excellence

Thank you.

Recent NICE appraisals for Duchenne muscular dystrophy

Recent NICE appraisals

Technology appraisal	Drug	Recommendation
HST22 (Feb 2023)	Ataluren	Recommended as an option for treating Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene in people 2 years and over who can walk

Abbreviations: HST, highly specialised technology.

Decision problem

	Final scope	Company submission	Comments
Population	Children and adults with Duchenne muscular dystrophy	In line with final scope	Considers children older than 4 years old
Intervention	Vamorolone	In line with final scope	
Comparators	Established clinical management without vamorolone	Partially in line with final scope	Efficacy and proportion of individual glucocorticoids (prednisone and deflazacort) important
Outcomes	Full outcomes listed in scope	Partially in line with final scope	Some outcomes not recorded in key vamorolone studies, deemed relevant to DMD but not expected in age group and follow-up of studies. Company did not collect EQ-5D.
Economic analysis	Reference case	Partially in line with final scope	Out-of-scope costs excluded by EAG.

Notes: Full decision problem and comments provided in EAG report.
Abbreviations: DMD, Duchenne muscular dystrophy; EAG, external assessment group; EQ-5D, EuroQol 5-dimension.

VISION-DMD baseline characteristics

VISION-DMD potentially limited generalisability, but model uses alternative data

Baseline characteristics

Characteristic	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)
Age (years), mean (SD)	5.54 (0.86)	5.42 (0.88)
Weight (kg), mean (SD)	21 (3)	19 (3)
Height (cm), mean (SD)	111 (6)	107 (7)
TTSTAND velocity (rises/sec), mean (SD)	0.22 (0.06)	0.19 (0.06)
6MWT distance (metres), mean (SD)	343.32 (55.84)	312.50 (56.19)
NSAA total score	21.16 (5.45)	18.86 (4.07)

Notes: Placebo and vamorolone 2.0 mg/kg/day not used in model so baseline characteristics not provided here.

EAG comments

- Multicentre VISION-DMD trial potentially had limited generalisability with only 6 of 33 centres from UK
- Company use an average starting age in the model of 4.1 years, based on a UK study by Vry et al. 2016, consistent with starting age in license of 4 years (sensitivity analysis increased age to 5.1 years)

Abbreviations: 6MWT, six-minute walking test; cm, centimetre; EAG, external assessment group; kg, kilogram; mg, milligram; n, number; NSAA, North Star Ambulatory Assessment; TTSTAND, time to stand; SD, standard deviation; UK, United Kingdom.

VISION-DMD results – muscle function (3)

Vamorolone muscle efficacy numerically lower than prednisone, not significant

	TTRW velocity change from baseline, metres/sec		TTCLIMB velocity change from baseline, step/sec	
	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	1.90 (0.43)	1.60 (0.36)	0.29 (0.11)	0.21 (0.09)
Week 24, mean (SD)	2.25 (0.43)	1.89 (0.41)	0.41 (0.16)	0.27 (0.10)
CFB at Week 24, mean (SD)	0.34 (0.24)	0.28 (0.28)	0.11 (0.10)	0.07 (0.06)
LSM (SE) change from baseline	0.37 (0.05)	0.26 (0.05)	0.11 (0.01)	0.06 (0.01)
LSM difference (SE) vs prednisone	NA	-0.11 (0.08)	NA	-0.05 (0.02)
95% CI vs prednisone	NA	-0.26, 0.04	NA	-0.09, -0.01
p-value vs prednisone	NA	0.1381	NA	0.0193
	NSAA score change from baseline		Knee extension muscle strength change from baseline to Week 24	
	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)	Prednisone (n=31)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	21.2 (5.45)	18.9 (4.07)	6.13 (1.41)	5.47 (1.74)
Week 24, mean (SD)	25.6 (5.47)	22.0 (5.17)	6.89 (1.86)	5.52 (2.22)
CFB at Week 24, mean (SD)	4.5 (3.66)	3.2 (3.18)	0.85 (1.57)	0.28 (1.93)
LSM (SE) change from baseline	4.29 (0.60)	2.85 (0.61)	1.01 (0.34)	0.01 (0.36)
LSM difference (SE) vs prednisone	NA	-1.44 (0.83)	NA	-0.91 (0.48)
95% CI vs prednisone	NA	-3.09, 0.20	NA	-1.87, 0.05
p-value vs prednisone	NA	0.0848	NA	0.0617

Abbreviations: CI, confidence interval; cm, centimetre; EAG, external assessment group; kg, kilogram; mg, milligram; n, number; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SE, standard error; TTCLIMB, time to climb; TTRW, time to run/walk 10 metres.

Long-term discontinuation

Long-term discontinuation uncertain, alternative assumptions have large impact on cost effectiveness

Landmark time estimates for unadjusted time on treatment extrapolations

Year	Vamorolone	Deflazacourt (15%)	Prednisone (85%)	SoC
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]

How should discontinuation of vamorolone be modelled?

Abbreviations: SoC, standard of care.

AE rates applied in model

Adverse events	Health state	Spinal vertebral fractures	Other fracture	Weight gain	Behav. issues	Cushingoid effects	Immune supressed/ infection	GI symptoms	Diabetes	Skin/ Hair change	Stunted Growth
Vam	Early ambulatory	0.00%	0.05%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00%
	Late ambulatory	0.00%	0.08%								0.00%
	Transfer	0.05%	0.00%								0.00%
	HTMF, no ventilation	0.56%	0.33%								0.00%
	No HTMF, no ventilation	0.31%	0.09%								0.00%
	HTMF, night-time ventilation	0.31%	0.09%								0.00%
	No HTMF, night-time ventilation	0.31%	0.09%								0.00%
	Full time ventilation	0.31%	0.09%								0.00%
SoC	Early ambulatory	0.00%	0.13%								1.75%
	Late ambulatory	0.00%	0.20%								1.75%
	Transfer	0.13%	0.00%								1.75%
	HTMF, no ventilation	1.36%	0.79%								1.75%
	No HTMF, no ventilation	0.83%	0.22%								1.75%
	HTMF, night-time ventilation	0.83%	0.22%								1.75%
	No HTMF, night-time ventilation	0.83%	0.22%								1.75%
	Full time ventilation	0.83%	0.22%								1.75%

Key issue: Blended comparator

EAG believe an incremental analysis between comparators is appropriate

Background

- Comparators limited to established clinical management – glucocorticoids (prednisone and deflazacort)
- VISION-DMD compared to prednisone 0.75 mg/kg/day or placebo

Company

- Primary comparator in base case was SoC, assumed to be a mixture of prednisone and deflazacort
- For drug costs, split assumed to be 85% prednisone and 15% deflazacort

EAG comments

- Concerns pooling comparators, introduces scope for gaming and evading relevant comparisons along the efficacy frontier
- Split not consistent for AEs, fractures and surgeries – differences between costs and outcomes
- Prednisone and deflazacort have distinct efficacy/safety, better to capture AEs separately where possible
- EAG compared to each separately, allowing a relatively clear distinction of between SoC treatments
- Preferred discrete treatment strategies compared in fully incremental analysis; applied 50/50 split in scenario

Is it appropriate to group corticosteroids or should they be considered individually? If appropriate, what is the expected split?

Abbreviations: AE, adverse event; DMD, Duchenne muscular dystrophy; EAG, external assessment group; kg, kilogram; mg, milligram; SoC, standard of care; UK, United Kingdom.

Key issue: Out-of-scope costs

EAG excluded non-reference case costs

Background

- NICE reference case specifies costs should be of NHS and personal social services perspective only

Company

- Costs included in the model to match reference case, however, also included additional costs, including:
  - Patient out of pocket costs (OTC medications, transport and alternative and complementary therapies)
  - Transfer payments (described as direct non-medical costs)

EAG

- Excluded out-of-scope costs, to limit the perspective to the NICE reference case
  - Approach could increase or decrease the ICER, depending on relative time spent in each health state in each arm

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; OTC, over the counter.

Key issue: Severity

Company and EAG base cases result in different severity weightings

Background

- NICE methods now include a QALY weighting system based on disease severity, but company and EAG estimates of severity differ

Company

- QALY shortfall calculator estimated absolute shortfall of 18.02 years and proportional shortfall of 72.37%
- Base case used a 1.7x QALY multiplier, based on an absolute QALY shortfall of 18.02 years

EAG and technical team comments

- Believed company estimate subject to high uncertainty; noted substantial impact on cost-effectiveness results
- General population QALYs derived using EQ-5D-3L but QALYs for people with DMD derived using DMD-QoL
  - Use of different utility instruments (generic vs disease specific) increases uncertainty
- Given uncertainty around modifier and likelihood of QALY shortfall between 12-18 years, used a 1.2x modifier
- Availability of mapping between DMD-QoL and EQ-5D-3L might help resolve this uncertainty
- Company severity conclusions on the margin of x1.7 and x1.2 threshold and impacted by starting age (e.g. starting age of 4 years gives x1.7 but 5 years gives x1.2), highlights uncertainty

Should a severity weighting be applied? If so, which weight?

NICE **Abbreviations:** DMD, Duchenne muscular dystrophy; EAG, external assessment group; EQ-5D-3L, EuroQol 5-dimension 3-level; QALY, quality-adjusted life-year; QoL, quality of life; SoC, standard of care.