Vamorolone for treating Duchenne muscular dystrophy

For public – confidential information redacted

Technology appraisal committee C [5th March 2024]

Chair: Richard Nicholas

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External assessment group: Peninsula technology assessment group (PenTAG)

Technical team: Lewis Ralph, Alan Moore, Ian Watson

Company: Santhera

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

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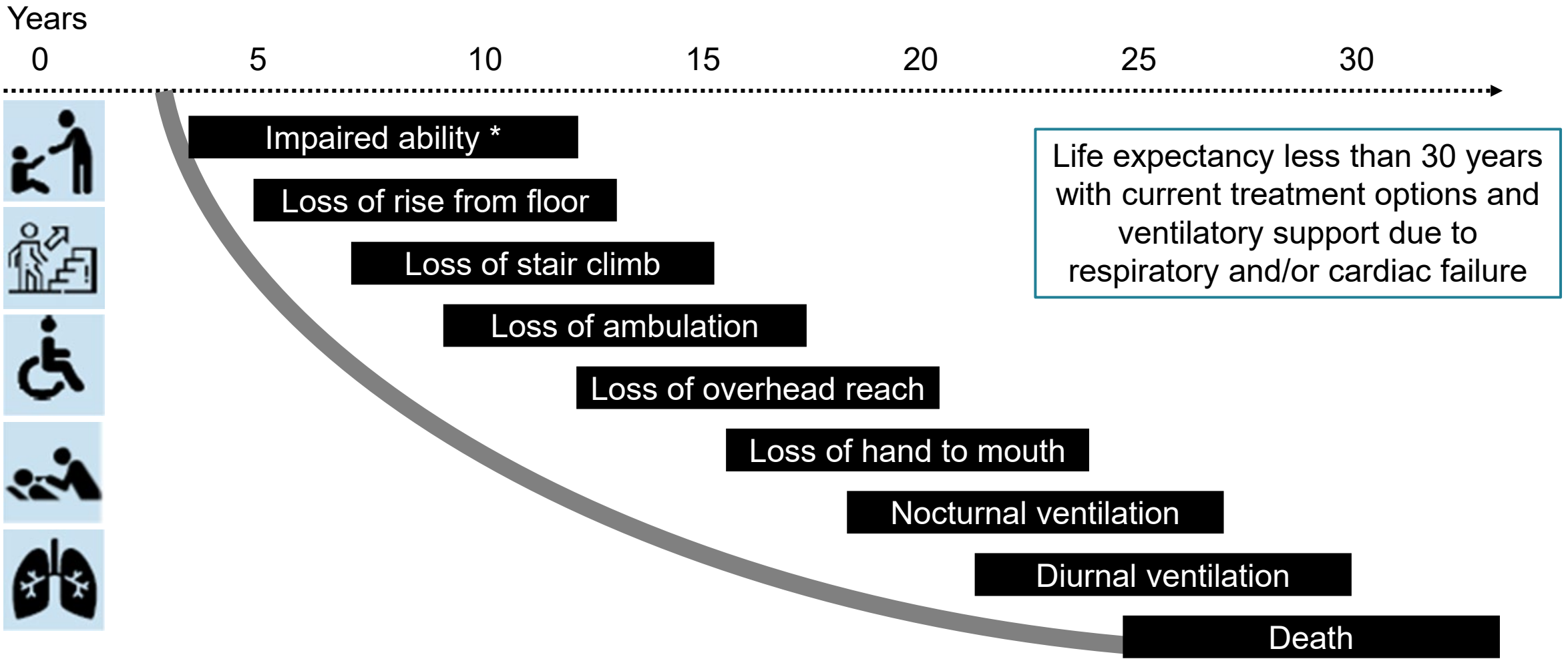
Abbreviations: DMD, Duchenne muscular dystrophy; UK, United Kingdom.

Natural disease course – stylised

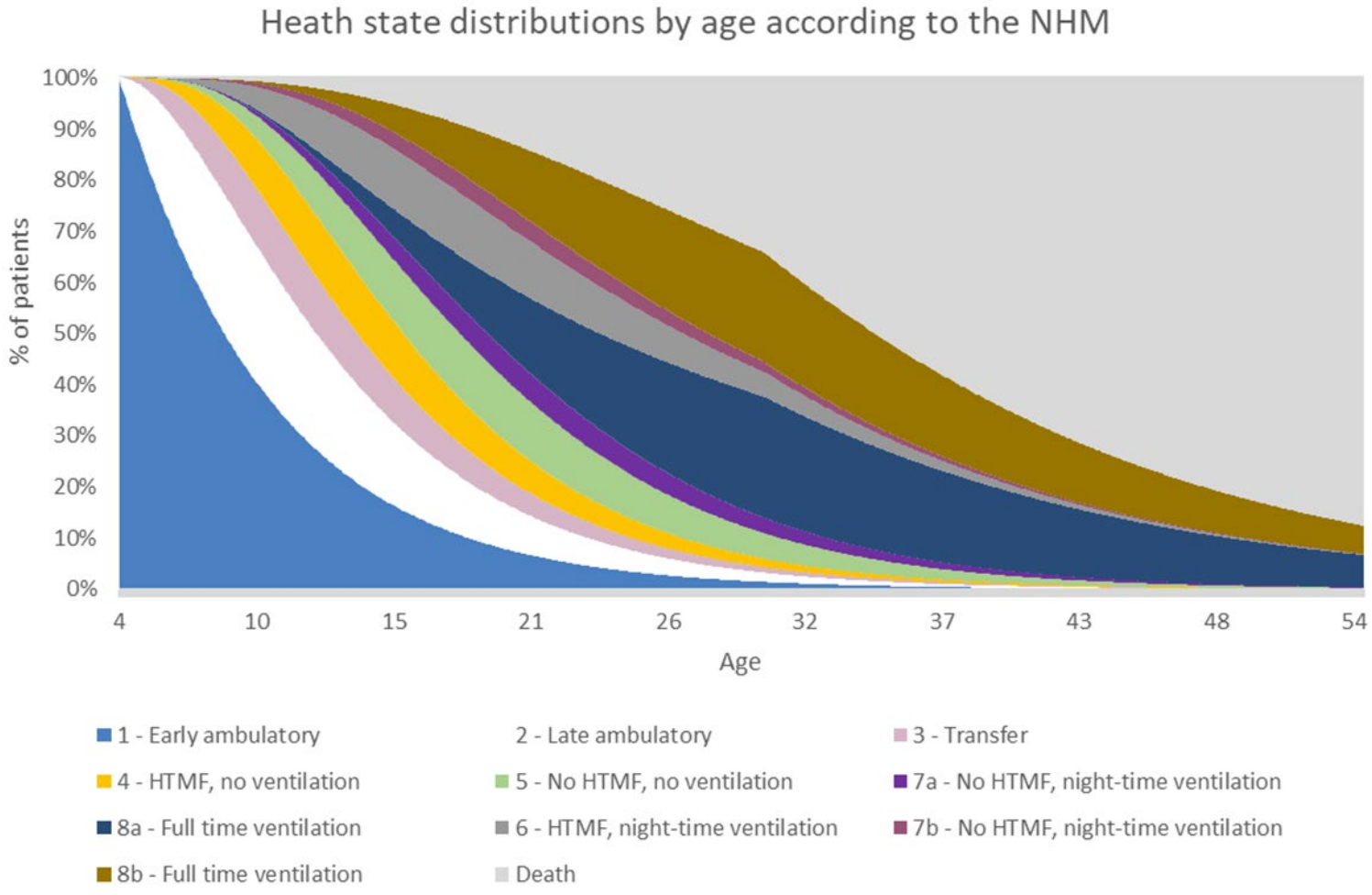
Typical muscle degeneration seen in people with Duchenne muscular dystrophy



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

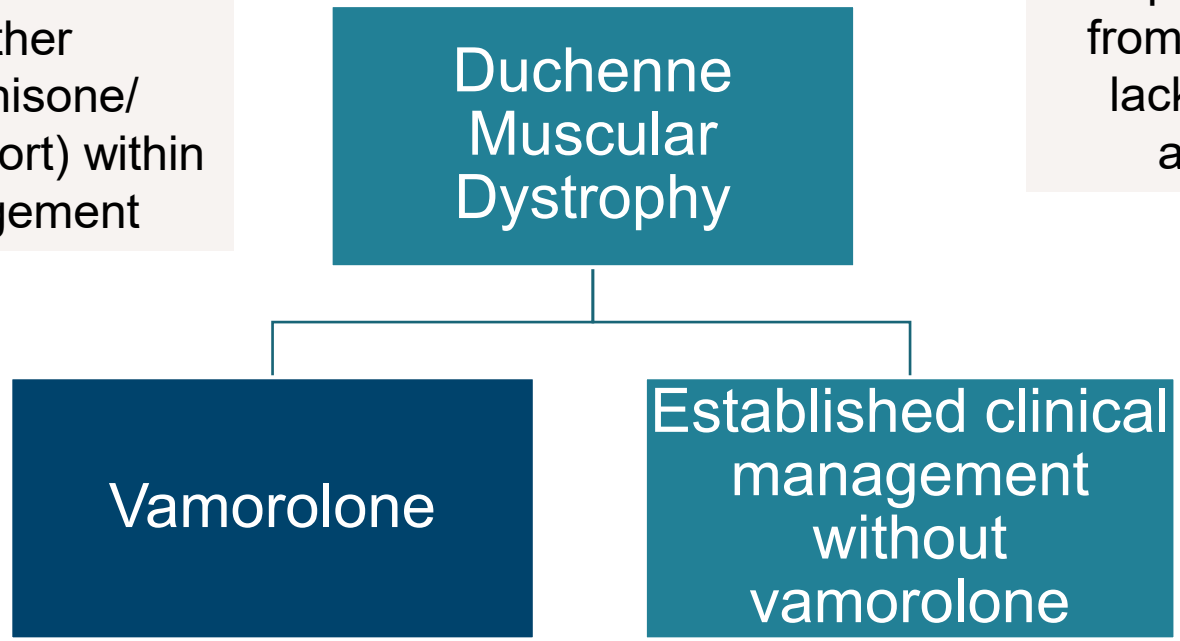
Does the natural history model reflect clinical outcomes for people with DMD in the UK?

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"

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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"

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

NICE National Institute for Health and Care Excellence

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

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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?

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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?

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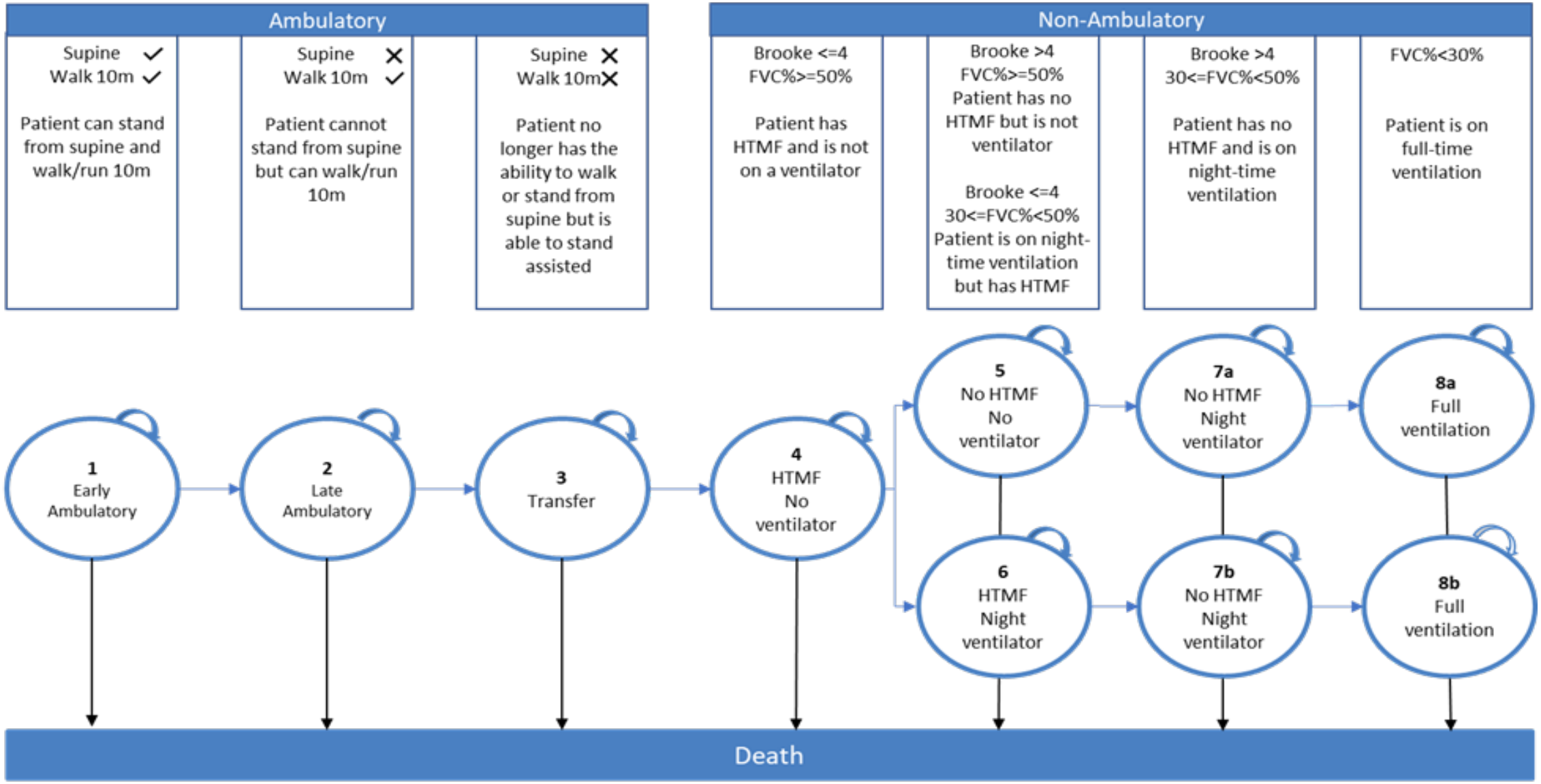
Abbreviations: ABM, Associate of British Neurologists; DMD, Duchenne muscular dystrophy; EAG, external assessment group; UK, United Kingdom.

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.

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?

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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

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

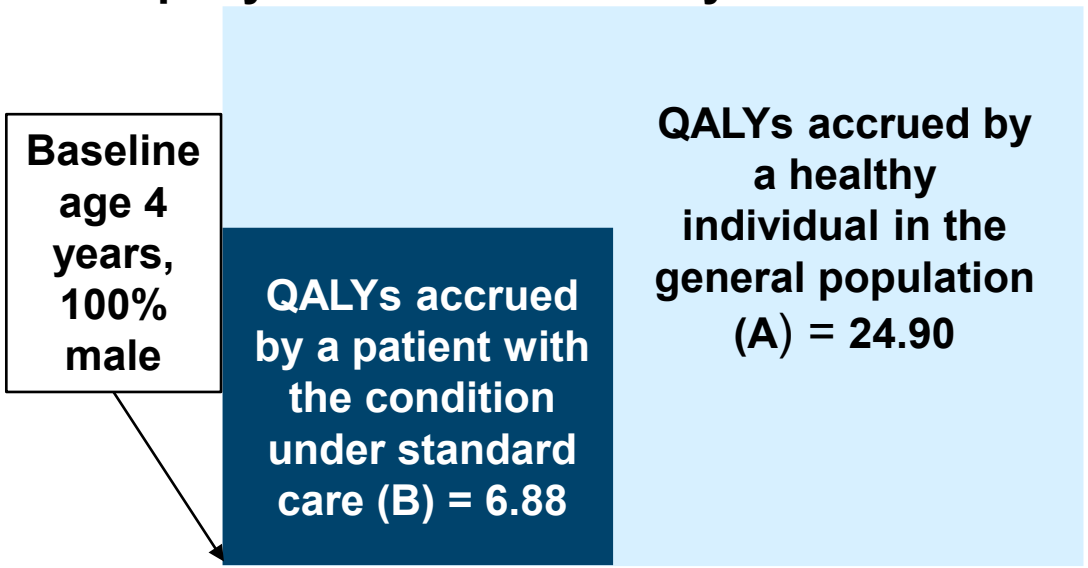
Abbreviations: AE, adverse event; BOI, burden of illness; EAG, external assessment group; HTMF, hand-to-mouth function; QALY, quality-adjusted life-year; SoC, standard of care.

QALY weighting for severity

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

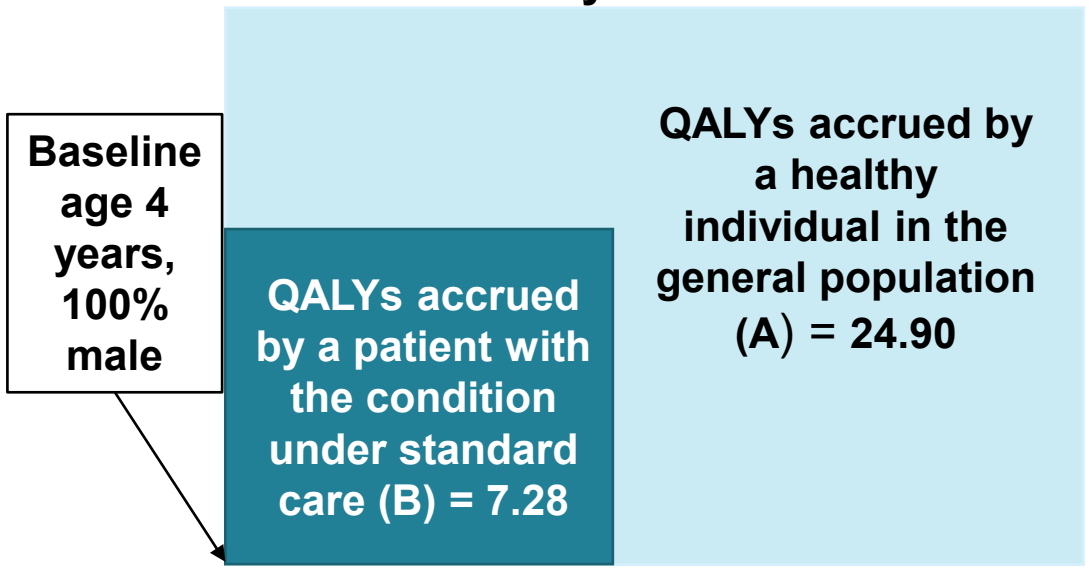
Note: VISION-DMD SoC mean age 5.54

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

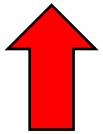
- Primary comparator in base case was SoC, assumed to be 85% prednisone and 15% deflazacort
- EAG concerned pooling evades relevant comparisons along the efficacy frontier
- Prednisone and deflazacort have distinct efficacy/safety profiles, differences between costs and outcomes
- EAG compared to each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

NICE **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%	0.00%	0.00%	0.66%	0.00%	0.00%	0.00%	0.00%	0.00%
	Late ambulatory	0.00%	0.08%	0.00%	0.00%	0.66%	0.00%	0.00%	0.00%	0.00%	0.00%
	Transfer	0.05%	0.00%	0.00%	0.00%	0.66%	0.00%	0.00%	0.00%	0.00%	0.00%
	HTMF, no ventilation	0.56%	0.33%	0.00%	0.00%	0.66%	0.00%	0.00%	0.00%	0.00%	0.00%
	No HTMF, no ventilation	0.31%	0.09%	0.00%	0.00%	0.66%	0.00%	0.00%	0.00%	0.00%	0.00%
	HTMF, night-time ventilation	0.31%	0.09%	0.00%	0.00%	0.66%	0.00%	0.00%	0.00%	0.00%	0.00%
	No HTMF, night-time ventilation	0.31%	0.09%	0.00%	0.00%	0.66%	0.00%	0.00%	0.00%	0.00%	0.00%
	Full time ventilation	0.31%	0.09%	0.00%	0.00%	0.66%	0.00%	0.00%	0.00%	0.00%	0.00%
SoC	Early ambulatory	0.00%	0.13%	0.59%	5.26%	0.00%	2.47%	0.59%	0.00%	0.59%	1.75%
	Late ambulatory	0.00%	0.20%	0.59%	5.26%	0.00%	2.47%	0.59%	0.00%	0.59%	1.75%
	Transfer	0.13%	0.00%	0.59%	5.26%	0.00%	2.47%	0.59%	0.00%	0.59%	1.75%
	HTMF, no ventilation	1.36%	0.79%	0.59%	5.26%	0.00%	2.47%	0.59%	0.00%	0.59%	1.75%
	No HTMF, no ventilation	0.83%	0.22%	0.59%	5.26%	0.00%	2.47%	0.59%	0.00%	0.59%	1.75%
	HTMF, night-time ventilation	0.83%	0.22%	0.59%	5.26%	0.00%	2.47%	0.59%	0.00%	0.59%	1.75%
	No HTMF, night-time ventilation	0.83%	0.22%	0.59%	5.26%	0.00%	2.47%	0.59%	0.00%	0.59%	1.75%
	Full time ventilation	0.83%	0.22%	0.59%	5.26%	0.00%	2.47%	0.59%	0.00%	0.59%	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.