Vamorolone [ID4024]: For treating inflammation associated with Duchenne muscular dystrophy

A Single Technology Appraisal

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Edward C. F. Wilson	Project director. Conducted additional economic analyses and drafted sections of the report

Table of Contents

List of key issues

List of tables

List of Figures

Abbreviations

Acronym	Definition
6MWT	Six-minute walk test
ACE	Angiotensin-converting enzyme
AE	Adverse effect
AESI	Adverse event of special interest
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BOI	Burden of illness
CEA	Cost effectiveness analysis
CEM	Coarsened exact matching
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for AEs
DMD	Duchenne muscular dystrophy
DNHS	Duchenne Natural History Study
EAG	External Assessment Group
EEACT	Economic Evaluation alongside Clinical Trials
EMA	European Medicines Agency
FDA	Food and Drug Administration
FVC	Forced Vital Capacity (expressed as % of predicted)
GC	Glucocorticoid
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTMF	Hand-to-mouth function
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IxRS	Interactive voice/web Response System

Acronym	Definition
KM	Kaplan Meier
LSM	Least squares mean
LYG	Life years gained
MAR	Missing at random
MCID	Minimal clinically important different
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intention to treat
MMRM	Mixed model repeated measures
MNAR	Missing not at random
NA	Not applicable
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NH	Natural history
NHB	Net Health Benefit
NHM	Natural history model
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NSAA	North Star Ambulatory Assessment
NSUK	North Star UK
OWSA	One-way sensitivity analyses
PARS	Psychosocial Adjustment and Role Skills
PAS	Patient access scheme
PD	Pharmacodynamic
PICO	Population Intervention Comparator Outcome
PIP	Paediatric investigational plan
PK	Pharmacokinetic
PODCI	Paediatric Outcomes Data Collection Instrument
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	Quality assessment

Acronym	Definition
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse effect
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SoC	Standard of care
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAE	Treatment-emergent adverse events
TSQM	Treatment Satisfaction Questionnaire
TTCLIMB	Time to climb four stairs
TTRW	Time to run or walk 10 metres
TTSTAND	Time to stand from supine
UK	United Kingdom

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3 to 1.6.

Broadly speaking, the key clinical issues related to the company's conclusion that vamorolone is equally effective as prednisone (SoC) and a lack of evidence linked to the sequencing of glucocorticoid treatments. In terms of cost effectiveness issues, the EAG noted that there was uncertainty surrounding: the company's approach to modelling standard of care (SoC); the estimation of the proportion of patients remaining on treatment over time; and the long-term impact of vamorolone on outcomes, particularly growth. The EAG also questioned the appropriateness of the stopping rule for vamorolone. Finally, the company's base case included a number of non-reference case items when estimating health state costs.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
#1	The EAG disagreed with the company's conclusion that vamorolone was equally effective as existing treatments	3.2.3.1, 3.5, 4.2.6
#2	Children on DMD may change steroid treatment due to efficacy and adverse effects, but treatment sequencing has not been included in the economic model	2.4, 3.2.2.2, 3.2.3.2, 3.5

ID	Summary of issues	Report sections
#3	The use of a blended comparator created uncertainty in cost effectiveness estimates	4.2.4, 6.2.2, 6.3
#4	There was inconsistency in efficacy assumptions between vamorolone and SoC following dose reduction	4.2.6, 6.3
#5	There was uncertainty about long-term discontinuation rates for vamorolone	3.2.2.2, 3.2.3, 4.2.6, **Error! Reference source not found.**, 6.3
#6	There was uncertainty over long-term stunted growth and behavioural outcomes following vamorolone	3.2.3, 4.2.6, 6.2.6, 6.3
#7	The company used a 1.7x QALY severity multiplier in the model, while the EAG believed that a 1.2x multiplier was more appropriate	4.2.6, 6.2.7, 6.3, 7
#8	The company included a large number of out-of-scope / non-reference case costs in its base case analysis for health state costs	4.2.8, 6.2.9, 6.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
The use of a blended comparator and the definition of SoC (85:15 pred:def) not applied consistently	Company assumed a blended comparison for SoC which consisted of 85% receiving prednisone and 15% receiving deflazacort. However, it has not been consistently applied across drug costs and adverse events in the model.	The EAG preferred to compare vamorolone to each individual treatment in a fully incremental analysis.	1.2, 1.5, 4.2.4, 6.2.2, 6.3
Limited short-term trial data on vamorolone discontinuation	The company's base case accounted for vamorolone discontinuation based on VISION-DMD short-term (<1 year) trial data, which is subject to high uncertainty in the long term.	The EAG assumed that the proportion of patients discontinuing vamorolone would be the same as CINRG data for deflazacort in the long term	1.2, 1.5, 4.2.6, 6.2.4, 6.3
Parametric extrapolation of proportion of patients	In the company's base case analysis, the proportion of patients on vamorolone and SoC were estimated by fitting independent Log-	EAG's preferred assumption implemented Generalised gamma parametric modelling to the proportion of patients discontinuing treatments.	1.2, 1.5, 4.2.6, **Error! Reference source not found.**, 6.3

	Company's preferred assumption	EAG preferred assumption	Report Sections
discontinuing vamorolone	logistic curves to each treatment arm.		
Down-titrated dose efficacy	In the company's base case, reduced transition probabilities were applied to people receiving SoC who had a dose reduction, whilst no reduction in effectiveness was applied to down-titrated vamorolone.	EAG's preferred assumption was to apply reduced effectiveness to reduced doses for both SoC and vamorolone. Modelling limitations meant the EAG eliminated the reduced effectiveness in SoC rather than applying the reduction to vamorolone.	1.2, 1.5, 4.2.6, 6.3
The proportion of vamorolone patients experiencing adverse events	The company assumed that the proportion of patients on vamorolone with stunted growth was 0% (based on 24-week data from VISION DMD).	Due to the lack of robust long-term clinical data, the EAG preferred to assume that a small proportion of patients on vamorolone (10% for All AESI and 5% for moderate/severe AESI) will experience stunted growth and 5% will experience behavioural issues as moderate/severe AESI.	1.2, 1.5, 4.2.6, **Error! Reference source not found.**, 6.3
Cost items	The company included non-medical and indirect costs in base case, and included of growth hormone costs	The EAG's preferred approach was the inclusion of only NHS+PSS costs, as per NICE reference case, and the exclusion of growth hormone costs on the basis of clinical opinion.	
QALY multiplier	1.7x was applied in the company's modelled base case	The EAG preferred to apply 1.2x in the EAG base case	1.2, 1.5, 4.2.6, 6.2.13, 6.3, 7

Abbreviations: AESI, Adverse event of special interest; CINRG, Cooperative International Neuromuscular Research Group; EAG, External Assessment Group; NHM, natural history model; QALY, quality-adjusted life year; SoC, standard of care

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing the number of adverse/acute events compared to SoC, thereby improving HRQoL and lengthening time on treatment.

Overall, the technology is modelled to affect costs by:

- Adding acquisition costs of vamorolone to the treatment pathway
- Offsetting downstream costs by reducing the number of adverse effects and their treatment costs (such as the use of growth hormone for stunted growth or the need for spinal surgery following vertebral fracture)

The modelling assumptions that have the greatest effect on the ICER are:

- Fully incremental comparison of vamorolone with prednisone and deflazacort (rather than a blended comparison)
- The rate of discontinuation of treatment for people using vamorolone and its parametric extrapolation in the long term
- The application of a symmetric effect of reduced dosing
- The rate of stunted growth and behavioural issues related moderate/severe AESI events with vamorolone in the long term

1.3. The decision problem: summary of the EAG's key issues

The EAG noted that a number of scoped outcomes for this appraisal were not captured in the evidence base for vamorolone. While the EAG considered that the absence of some of these outcomes led to uncertainty in the clinical effectiveness of vamorolone, clinical experts to the EAG advised that the outcomes available would be sufficient to determine whether vamorolone was effective and safe in the short term. The EAG therefore did not identify any key issues regarding the decision problem for this appraisal.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the clinical effectiveness and safety evidence presented in the CS and identified the following key issues for consideration by the committee.

Key Issue 1: The EAG disagreed with the company's conclusion that vamorolone was equally effective as existing treatments

Report sections	**3.2.3.1, 3.5, 4.2.6**
Description of issue and why the EAG has	In Section B.3.3.2 of the CS, the company suggested that vamorolone 6.0 mg/kg/day showed comparable efficacy to prednisone 0.75 mg/kg/day in

Report sections	3.2.3.1, 3.5, 4.2.6
identified it as important	VISION-DMD. The company used this conclusion to drive assumptions in its economic model. The EAG did not agree with this interpretation of the VISION-DMD data. Prednisone 0.75 mg/kg/day offered a benefit over vamorolone 6.0 mg/kg/day at 24 weeks for several clinical outcomes related to muscle function. These differences were interpreted by the EAG as being clinically meaningful to people with DMD. Therefore, the EAG considered that prednisone 0.75 mg/kg/day was consistently more effective than vamorolone 6.0 mg/kg/day for the efficacy outcomes reported, and an assumption of comparable efficacy was inappropriate.
What alternative approach has the EAG suggested?	The EAG considered that vamorolone may still be a valued treatment option for people with DMD, despite the potential risk that it may have poorer clinical outcomes related to muscle function. This was based on the understanding that vamorolone offers an alternative safety profile, that may be preferred for some people with DMD. Within the context of this appraisal, this key issue has more significant implications for the company's model, which did not capture the difference in clinical efficacy between vamorolone and SoC. The EAG was unable to address this during its appraisal.
What is the expected effect on the cost-effectiveness estimates?	If the company's model was amended to incorporate a clinical advantage for SoC, this would reduce the QALY gain for vamorolone and would be expected to substantially increase the ICER
What additional evidence or analyses might help to resolve this key issue?	Further comparative evidence between vamorolone and SoC, particularly at longer follow-up and including outcomes that assess the implications of any difference in clinical efficacy between arms, would provide clarity on any difference in treatment efficacy between arms. The EAG was aware that the company had conducted an indirect treatment comparison between VISION-DMD and another trial that evaluated SoC options, though only reported safety outcomes. If the company were able to provide a comparison of clinical outcomes from this analysis, that may provide further data beyond the 24-week comparison available in VISION-DMD. With regards to the economic model, the company could address this by utilising transition probabilities for vamorolone linked to the efficacy in the VISION-DMD trials rather than using those developed from the natural history model (NHM) dataset. The company noted in Section B.3.3.2 of the CS that this was not feasible due to the short follow-up of 24 weeks. However, the company could investigate approaches to extrapolation that were more suitable than using the NHM transition probabilities or alternatively applying the efficacy difference between vamorolone and prednisone in the VISION-DMD to the transition probabilities in the NHM.

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; CS, company submission, EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; MCID, minimal clinically important difference; NHM, natural history model; QALY, quality-adjusted life year; SoC, standard of care; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine.

Key Issue 2: Children on DMD may change steroid treatment due to efficacy and adverse effects, but treatment sequencing has not been included in the economic model

Report sections	**2.4, 3.2.2.2, 3.2.3.2, 3.5**
Description of issue and why the EAG has identified it as important	The decision of whether to use prednisone/prednisolone or deflazacort as the initial therapy for DMD is largely based on parent preferences related to the expected efficacy and side effects for each treatment (and the broader health and wellbeing of the person with DMD). Typically, prednisone/prednisolone is associated with weight gain, increased appetite, and behavioural problems, while deflazacort is thought to lead to eye cataracts, a higher risk of stunted growth and extremely delayed puberty. Based on the CS, the EAG considered that vamorolone may be less effective than SoC but may have an improved safety profile for some adverse events. The EAG considered it plausible that vamorolone would be received at varying lines of treatment, depending on parent preferences. However, trial evidence for vamorolone is based on a treatment-naïve population and the EAG was unable to determine whether the effect of vamorolone would vary according to its positioning. In addition, the economic model was not structured to allow people to have a sequence of glucocorticoid treatments for DMD.
What alternative approach has the EAG suggested?	The EAG was unable to address this issue, given the VISION-DMD trial design and the structure of the company's economic model.
What is the expected effect on the cost-effectiveness estimates?	Given the lack of available evidence for varying treatment effects according to treatment line and the format of the company's model, the EAG was unable to speculate on the potential impact of this key issue on cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Within the timeframe of this appraisal, the EAG was unable to identify data points for clinical outcomes following treatment switching between prednisone and vamorolone in VISION-DMD, as these were not presented in the CS (aside from in charts). If the company was able to provide data for these outcomes, the EAG may be able to appraise their comparability with treatment outcomes in the first line population. However, the EAG was aware that these data would still be a partial and limited evaluation of this issue. Input from clinical experts as to whether treatment outcomes with SoC vary according to treatment line may be able to provide clarity on this issue. It would not be feasible to evaluate the impact of treatment sequences on cost effectiveness outcomes without structural changes to the company's economic model.

Abbreviations: EAG, External Assessment Group; DMD, Duchenne muscular dystrophy; SoC, standard of care.

1.5. The cost effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the cost-effectiveness and wider economic evidence presented in the CS and identified the following key issues for consideration by the committee.

Key Issue 3: The use of a blended comparator created uncertainty in cost effectiveness estimates

Report sections	4.2.4, 6.2.2, 6.3
Description of issue and why the EAG has identified it as important	In the company's base case analysis, the primary comparator was SoC, which was assumed to be a mixture of prednisone and deflazacort. For the estimation of drug costs, the split was assumed to be 85% for prednisone and 15% for deflazacort. However, this split was not used consistently for the estimation of adverse/acute events, vertebral fractures, and spinal surgeries. As such, there was dissonance between the company's modelling of comparator treatment costs and their approach to modelling impact of adverse/acute events, vertebral fractures, and spinal surgeries. Clinical expert opinion to the EAG also noted that prednisone and deflazacort have distinct safety profiles, suggesting that it may be more appropriate to capture the adverse event impact of each treatment separately in the model, where possible. Therefore, the EAG did not consider that the company's approach to modelling the comparators in a blended way was appropriate, as it ignored the differences between prednisone and deflazacort in terms of their efficacy and safety profiles, adds uncertainty to the results and potentially biases the analysis in favour of vamorolone.
What alternative approach has the EAG suggested?	Where possible within the current model framework, the EAG compared vamorolone to each corticosteroid separately. This allowed for a relatively clear distinction of safety profile between SoC treatments and reduced the associated uncertainty as part as was feasible. This was considered as part of the EAG preferred base case. Clinical expert opinion to the EAG was that, in clinical practice in the NHS, there was an approximately 50/50 split in the use of prednisone and deflazacort. The EAG therefore conducted a scenario analysis using a blended comparator treatment split of 50% prednisone and 50% deflazacort, though, overall, retained its preference for separate comparators.
What is the expected effect on the cost-effectiveness estimates?	A tangible increase in the ICER was observed, mainly owing to the differences in safety between prednisone and deflazacort. This was seen despite similar drug acquisition costs and clinical efficacy assumptions between the SoC treatments.
What additional evidence or analyses might help to resolve this key issue?	Providing an individual comparison of vamorolone versus prednisone and deflazacort using respective clinical efficacy and adverse event data would help to resolve the uncertainty further.

Abbreviations: EAG, External Assessment Group; GC, glucocorticoid; ICER, Incremental cost-effectiveness ratio; SoC, standard of care.

Key Issue 4: There was inconsistency in efficacy assumptions between vamorolone and SoC following dose reduction

Report sections	4.2.6, 6.3
Description of issue and why the EAG has	The company's base case applied proportionally reduced transition probabilities for SoC patients who were on treatment following a dose reduction but did not apply this to vamorolone patients who similarly down-

Report sections	4.2.6, 6.3
identified it as important	titrated. The EAG considered this asymmetry to be inappropriate and to overestimate the QALY gain from vamorolone whilst reducing its cost.
What alternative approach has the EAG suggested?	The EAG applied SoC efficacy and transition probabilities for patients who down-titrated on SoC in line with the assumption for vamorolone (i.e., no impact on efficacy from down-titration). The EAG acknowledged that, in reality, there would likely be a reduction in efficacy following down titration with SoC and vamorolone, but due to the structure of the model there was no robust way of implementing this. This was implemented in the model by setting the proportion on treatment receiving full efficacy to the same as the proportion on treatment for the SoC arm (in a similar way to how it was implemented for vamorolone in the company's modelled base case).
What is the expected effect on the cost-effectiveness estimates?	This change resulted in an increase of health state related QALY gain for the SoC arm, thereby causing a reduction in incremental QALYs and a tangible upward impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Availability of long-term studies on efficacy of reduced dosing of SoC could help to reduce this uncertainty further.

Abbreviations: EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Key Issue 5: There was uncertainty about long-term discontinuation rates for vamorolone

Report sections	**3.2.2.2, 3.2.3, 4.2.6,** Error! Reference source not found.**, 6.3**
Description of issue and why the EAG has identified it as important	The EAG noted that data for the number of people who discontinue vamorolone were only available for a short duration (<1 year), based on the VISION-DMD trial data. There was therefore some uncertainty in the likely discontinuation rate beyond this time. The company's method for extrapolating these short-term data provided some advantage for vamorolone in the model, which the EAG did not consider was justified on the basis of the evidence available. This uncertainly was especially acute given that the comparator arm (SoC) had discontinuation data available for ~14 years, derived from CINRG. Also, in the company's modelled base case analysis, the proportion of patients on vamorolone and SoC were estimated by fitting independent Log-logistic curves to each treatment arm. However, the EAG considered generalised gamma to be best fitting curve for SoC, given it aligned more closely with prednisone and deflazacort KM data. This was implemented as part of the EAG preferred base case as this was linked to the treatment discontinuation data used for the modelled EAG base case.
What alternative approach has the EAG suggested?	The EAG assumed that the proportion of patients discontinuing vamorolone would be the same as CINRG data for deflazacort in the long term. Deflazacort arm data was chosen as its KM curve closely resembled that of vamorolone (based on EAP data presented in the clarification response) and improved adherence might be expected given the claim of better side effect profile for vamorolone.

Report sections	**3.2.2.2, 3.2.3, 4.2.6,** Error! Reference source not found.**, 6.3**
	In terms of the parametric fit, the EAG implemented generalised gamma modelling of the proportion of patients discontinuing treatments and applied deflazacort discontinuation data based on CINRG for vamorolone.
What is the expected effect on the cost-effectiveness estimates?	This change substantially increased the ICER due to the higher proportion of patients remaining on vamorolone in the long term. This was despite the generalised gamma curve predicting a slightly lower proportion of patients discontinuing with time across treatment arms, resulting in increased treatment costs for vamorolone as well as the health state related QALY gain. However, the net effect was increased incremental costs, which could not be offset by the corresponding increase in the incremental QALYs, thereby resulting in an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	Long-term treatment discontinuation data for vamorolone would help address this uncertainty.

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Key Issue 6: There was uncertainty over long-term stunted growth and behavioural outcomes following vamorolone

Report sections	**3.2.3, 4.2.6,** Error! Reference source not found.**, 6.3**
Description of issue and why the EAG has identified it as important	Stunted growth and behavioural issues are known side effects of existing SoC for DMD. In the company's base case, 72% of patients in the SoC arm were modelled to experience stunted growth, as opposed to 0% of patients in the vamorolone arm. This was based on 24-week data reported in VISION-DMD. Additionally, 0% of patients on vamorolone were modelled by the company to have behavioural issues as moderate/severe adverse events (also based on 24-week data from VISION-DMD). The EAG considered there to be some uncertainty surrounding these assumptions, given that they were based on short-term follow-up. Clinical advice to the EAG also noted that stunted growth could manifest in later years of life.
What alternative approach has the EAG suggested?	In the absence of robust long-term data, the EAG opted to assume that a small proportion of patients on vamorolone (10% for All AESI and 5% for moderate/severe AESI) will experience stunted growth and 5% will experience behavioural issues as moderate/severe AESI. These assumptions were included as part of the EAG's preferred base case. The EAG also conducted a scenario analysis with the vamorolone arm having the same proportion of stunted growth and behavioural issues as with SoC. This was considered to be a worst-case scenario, compared to the company's modelled base case, which presented the best-case scenario (that of a proportion of 0%). These two scenarios therefore provided an upper and lower bound, with the most plausible values lying in-between.
What is the expected effect on the cost-	The EAG observed that this change increased the ICER moderately, due to the modelled cost and disutility associated with stunted growth and behavioural issues.

Report sections	**3.2.3, 4.2.6,** Error! Reference source not found.**, 6.3**
effectiveness estimates?	
What additional evidence or analyses might help to resolve this key issue?	Longer term clinical data reporting the impact of vamorolone on patient growth and behaviour, or other impactful AEs, would help to resolve this uncertainty.

Abbreviations: AESI, Adverse event of special interest; DMD, Duchenne muscular dystrophy; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; SoC, standard of care

Key Issue 7: The company used a 1.7x QALY severity multiplier in the model, while the EAG believed that a 1.2x multiplier was more appropriate

Report sections	**4.2.6, 6.2.13, 6.3, 7**
Description of issue and why the EAG has identified it as important	The company's base case used a 1.7x QALY multiplier, based on an absolute QALY shortfall of 18.02 years. The EAG believed that this was subject to high uncertainty and noted that it had a substantial impact on the cost-effectiveness results. Also, the expected total QALYs for the general population were derived using EQ-5D-3L while the total QALYs for people living with the condition receiving SoC were derived using DMD-QoL. Given the different QoL instruments used, one being generic and the other being disease specific, this further increased the uncertainty in the QALY shortfall estimate.
What alternative approach has the EAG suggested?	Given the high uncertainty around the modifier and the likelihood of QALY shortfall falling between 12-18 years in the EAG base case, a QALY multiplier of 1.2x was considered. The EAG also conducted a scenario analysis with 1x QALY multiplier, as there was a chance that the absolute QALY shortfall would fall below 12 years, given the associated uncertainties.
What is the expected effect on the cost-effectiveness estimates?	Reducing the QALY multiplier from 1.7 to 1.2 substantially increased the ICER due to reduction in the incremental QALY gain.
What additional evidence or analyses might help to resolve this key issue?	Availability of mapping between DMD-QoL and EQ-5D-3L, might help to resolve this uncertainty further.

Abbreviations: EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Key Issue 8: The company included a large number of out-of-scope / non-reference case costs in its base case analysis for health state costs

Report sections	**4.2.8, 6.2.11, 6.3**
Description of issue and why the EAG has identified it as important	The NICE reference case specifies that cost perspective should be that of the NHS and personal social services (PSS) only. The company's costings for its reference case, however, included additional costs such as patient out of pocket costs (OTC medications, transport and alternative and complementary

Report sections	4.2.8, 6.2.11, 6.3
	therapies) and transfer payments (described as direct non-medical costs, Section B3.5.2, CS).
What alternative approach has the EAG suggested?	The EAG approach excluded out-of-scope costs, to limit the perspective to the NICE reference case.
What is the expected effect on the cost-effectiveness estimates?	The approach could bias the ICER either upwards or downwards, depending on the relative time spent in different health states in each arm.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence was required. The EAG modified the costs in its base case, limiting them to NHS and PSS costs only.

Abbreviations: CS, company submission; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

1.6. Other key issues: summary of the EAG's views

No other key issues were identified.

1.7. Summary of EAG's preferred assumptions and resulting ICER

Table 3 summarises the corrections (mainly to the severity modified QALYs and other corrections as mentioned in Section 6.1) and EAG-preferred changes to the company base case analysis, and their isolated and collective implications for cost-effectiveness results. The EAG's adjustments collectively reduced the expected incremental QALY gain associated with vamorolone while increasing its expected incremental cost, leading to EAG-preferred ICERs that were far in excess of the relevant NICE decision-making threshold range.

Table 3: Summary of EAG's preferred assumptions and ICER

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)
EAG corrected company base case					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symmetric impact of down-titration of treatment dose					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% stunted growth and behavioural issues with vamorolone in long-term					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation extrapolated using gen-gamma with vamorolone discontinuation assumed same as deflazacort CINRG data					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude out-of-scope costs					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude growth hormone costs					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.2x QALY multiplier applied					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (deterministic)					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (probabilistic)					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

This report contains the EAG's assessment of the company submission (CS) submitted for the Single Technology Appraisal (STA) of vamorolone (Agamree®, Santhera) for treating Duchenne muscular dystrophy in people aged four years and older.

2.2. Critique of the company's description of the underlying health problem

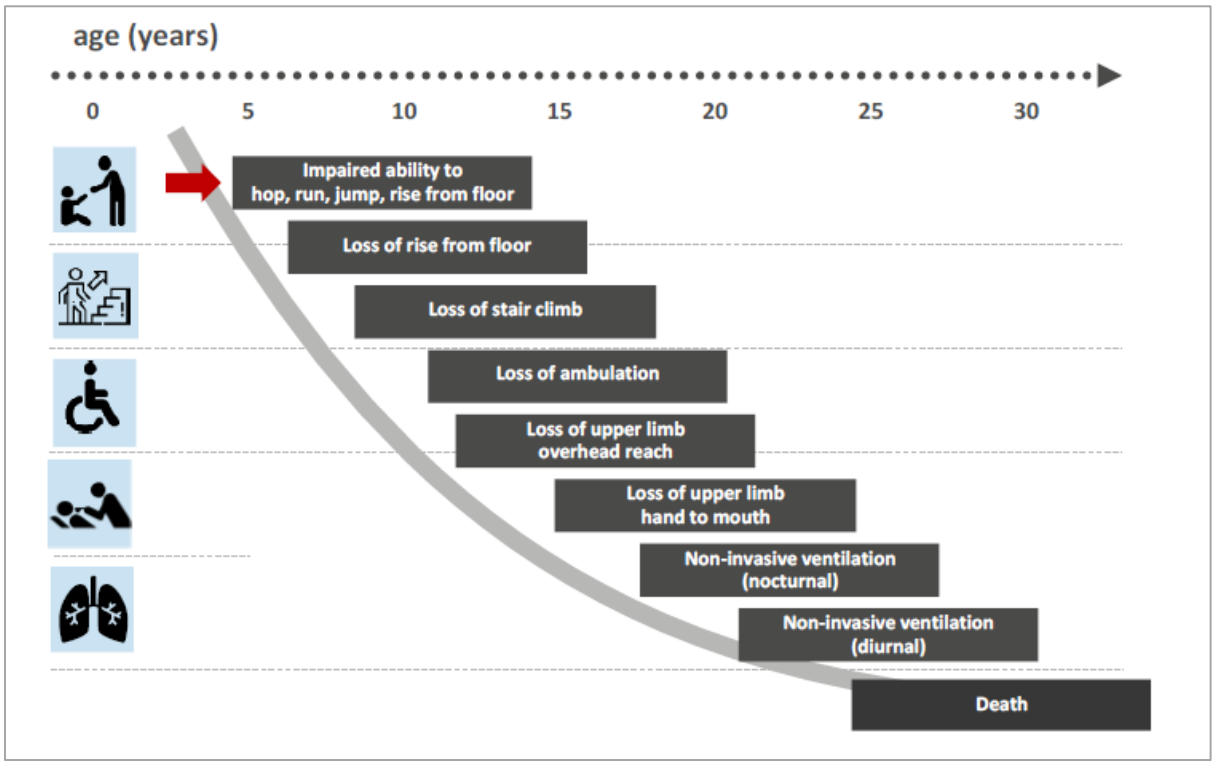
The EAG agreed with the company's description of Duchenne muscular dystrophy (DMD). In brief, DMD is a genetic disorder characterised by progressive muscle degeneration and weakness due to the alterations of a protein called dystrophin that helps keep muscle cells intact. This faulty gene can itself be caused by a range of genetic causes, such as deletions or duplications, point mutations, and nonsense mutations. The EAG's clinical experts advised that it is important to know exactly where the mutation is and what type of mutation it is to guide treatment. For example, people with DMD caused by the nonsense mutations are eligible for ataluren, in addition to standard of care.[1] Because the dystrophin gene is found on the X-chromosome, it primarily affects males, while females are typically carriers. However, some females can manifest varying ranges of physical symptoms of Duchenne and are therefore called "manifesting carriers".

DMD symptom onset is in early childhood, usually between ages 2 and 3. People with DMD begin to experience a decline in muscle strength in their hips and legs, leading to a loss of abilities such as running, climbing stairs, getting up from a lying position, and eventually, walking or bearing weight. As muscle strength decreases, weakness will spread to the arms and neck and over time, paralysis will set in, with the loss of arm and hand-function. Young adults can develop dysphagia, resulting in difficulty chewing and swallowing food and requiring a feeding tube. They will need help with all self-care activities, including eating, drinking, toileting, dressing, washing, being moved into bed, and being turned in bed. Respiratory function will also weaken as DMD progresses, leading to assisted ventilation, and the heart muscle will be affected, leading to cardiac failure. In Section B.1.3, the company highlighted the significant disease-related burden for patients, families and caregivers in terms of physical, health demands, logistical, emotional, psychological, and financial burden. Given that symptoms can

start presenting in children as young as two years old, people with DMD live their whole life with gradually increasing physical impairment and dependency on other people.

The company detailed the natural history of a person diagnosed with DMD who is treated with glucocorticoids in Figure 1 below. The aim of glucocorticoid treatment is to slow the progression of disease, and delay a person's loss of ambulation, ability to self-feed, and need for assisted ventilation.

Figure 1: Typical muscle degeneration seen in patients with DMD



Source: CS, Figure 2, Document B

2.3. Critique of the company's overview of current service provision

The company detailed the clinical pathway of care in Section B.1.3 of the CS. The EAG's clinical experts agreed with the company that DMD is a progressive disease and treatment goals are aimed at delaying disease progression for as long as possible, and to anticipate and manage the associated complications, such as joint contractures, scoliosis, bone fractures, cardiomyopathy, respiratory insufficiency and treatment-related adverse events (AEs).

The EAG agreed with the company that the current standard of care for DMD is glucocorticoids, specifically prednisone/prednisolone or deflazacort. Glucocorticoids have demonstrated significant benefits in minimising the progressive loss of muscular strength and consequently extending ambulatory function, avoiding scoliosis surgery, preserving upper limb function and delaying the start of cardiac and respiratory function decline. However, they are associated with severe side effects, which include osteoporosis, reduced bone strength and increased risk of vertebral fractures, resulting from the potent osteotoxicity of glucocorticoid therapy combined with progressive myopathy. The EAG's clinical experts advised that treatment with glucocorticoids currently starts in children at a point after they have turned four years old. The decision of whether to use prednisone/prednisolone or deflazacort is taken by the child's parents and is largely based on preferences related to the balance between the expected efficacy and side effects for each treatment. Typically, prednisone/prednisolone is associated with weight gain, increased appetite, and behavioural problems, while deflazacort is thought to lead to a longer period of ambulation, but with the risk of stunted growth and extremely delayed puberty. The EAG's clinical experts noted that people with DMD often have learning difficulties and autism spectrum disorders, and behavioural problems caused by prednisone may be exacerbated by the underlying disorders. In that case parents may choose to initially choose deflazacort treatment rather than prednisolone. However, parents can change the glucocorticoid and dose of glucocorticoid in response to adverse events. Notably for this appraisal, the EAG's clinical experts estimated that 50% of new prescriptions of glucocorticoids in the DMD population in the UK are for prednisolone and 50% are for deflazacort. The EAG's clinical experts advised that a very small proportion of parents of people with DMD may decline glucocorticoid treatment at the outset.

Aside from glucocorticoids, children may also receive vitamin D and gastroprotectives, such as ranitidine or omeprazole. There are other treatments, such as antisense oligonucleotides (ASOs) or monoclonal antibody therapy. These treatments are not suitable for all with DMD as they are exon skipping specific and their efficacy is currently unclear in the DMD population.

Glucocorticoid treatment has been shown to be effective at delaying the loss of ambulation in people with DMD: this can occur at around 10 years old in untreated children but it can occur more than two years later in those on glucocorticoid treatment.[2] The EAG's clinical experts noted that the primary reason for offering glucocorticoids to people with DMD is to prolong ambulation, and after loss of ambulation treatment can be reduced or withdrawn. In the CS, the company stated that glucocorticoid treatment can continue after loss of ambulation. The EAG

understood that in some occasions, treatment with glucocorticoids may be reduced rather than withdrawn because it may protect them from scoliosis and slow down both cardiomyopathy and decline in respiratory function.

The EAG's clinical experts advised that once children lose ambulation, care is taken to closely monitor their spines, sleep-disordered breathing and heart. The spine develops scoliosis, which needs its own management and may require scoliosis surgery. The heart develops cardiomyopathy, which may need treatment with ACE inhibitors and beta blockers. Sleep studies can be used to assess the development of respiratory failure. People will then require overnight non-invasive ventilation and cough assist to help clear their airways.

2.4. Critique of company's definition of decision problem

A summary of the decision problem for this appraisal, and the EAG's appraisal of how the CS addresses it, is shown in Table 4. The company positioned vamorolone as an alternative to glucocorticoids (prednisone/prednisolone or deflazacort) offered to people with DMD. As noted in Section 2.3, prednisone/prednisolone and deflazacort can offer significant benefits in slowing the progression of DMD but are also associated with severe adverse effects. The EAG's clinical experts stated that a drug that offered a similar benefit to prednisone/prednisolone or deflazacort in delaying loss of ambulation while having fewer significant adverse effects would be a valuable addition to the DMD treatment pathway.

The population for this appraisal began as people with DMD who are aged two years and older. However, after the company submission but prior to the clarification stage, marketing authorisation was granted by the European Medicines Agency (EMA) for vamorolone in people with DMD who are four years and older.[3] The MHRA is expected to grant marketing authorisation in line with the EMA decision, and the company updated the population for this appraisal. The EAG noted that the vamorolone trials used for this appraisal recruited children four years and older, and as such, provided evidence appropriate to the updated population in the appraisal.

The EAG noted that the children who were recruited to VISION-DMD were naïve to glucocorticoid treatment, while treatment line is not specified in the NICE scope for this appraisal or in the EMA marketing authorisation. The EAG's clinical experts were aware that people may receive vamorolone after previously receiving treatment with a different glucocorticoid, or alternatively might receive treatment with a different glucocorticoid after

previous treatment with vamorolone. The cost-effectiveness of treatment sequencing was not assessed in this appraisal or adequately explored in the pivotal trial (VISION-DMD). This issue is discussed further in Key Issue 2.

The company also stated that the population aged over 7 years of age is supported by an ongoing Phase II open-label, multiple dose trial (VBP15-006) to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with DMD. The EAG noted that no results were presented for VBP15-006 in the CS.

The intervention for this appraisal was consistent with the decision problem. The doses tested in the VISION-DMD, were in-line with the dose permitted in the EMA marketing authorisation.

The comparator in the final scope issued by NICE was established clinical management without vamorolone. The company interpreted this as standard of care (SoC) with either prednisone or deflazacort. The pivotal trial, VISION-DMD, compared daily vamorolone to daily prednisone and data specific to deflazacort was taken from other trials such as FOR-DMD.[4] The EAG's clinical experts stated that 50% of new prescriptions of glucocorticoids for DMD are deflazacort in the UK. The EAG understood that there were differences in efficacy and safety between prednisone and deflazacort and the comparison of deflazacort to vamorolone had not been explored in an RCT. The EAG did not consider that data collected in the prednisone arm of VISION-DMD to be a fair representation of outcomes experienced by people receiving SoC in the NHS. Specifically, outcomes in the CS may overestimate weight gain and behaviour problems and underestimate outcomes linked to eye cataracts and stunted growth. The company provided AESI and acute event rates for deflazacort from the FOR-DMD trial[4] at the clarification stage (Question B8), utilised fracture data from the Perera et al. (2016)[5] and stunted growth from Wong et al (2016)[6] to fill holes in the evidence space.

The final scope issued by NICE described 16 outcomes to be considered in the appraisal. The company stated that 7 of the 16 outcomes were directly measured in VISION-DMD but noted that lung and cardiac function were consequences of muscle function and time to wheelchair could be assessed through walking ability. The EAG's clinical experts advised that the outcomes collected in VISION-DMD represented the standard clinical outcomes used on a day-to-day basis and were appropriate given the stage of DMD of the participants in VISION-DMD.

Outcomes detailed in the scope that were not measured in VISION-DMD included, cardiac function, lung function, time to wheelchair, and time to scoliosis. VISION-DMD recruited children four to seven years old, and no loss of ambulation was expected in children until 10 years of age. Therefore, participants in the trial would not be expected to move to use of a wheelchair over the treatment period. People with DMD develop scoliosis after loss of ambulatory capacity and onset of wheelchair dependence for mobility. In addition, children diagnosed with DMD have a baseline cardiac assessment for an early cardiomyopathy, but close monitoring of heart and lungs does not occur until children lose ambulation. The EAG understood that the controlled trial period of VISION-DMD was 24 weeks in people with early DMD, and as such, the trial was not long enough to offer a robust estimate of cardiac function, lung function, time to wheelchair, or time to scoliosis.

The company did not collect health-related quality of life data using EQ-5D, the preferred measure of health-related quality of life in adults[7] in the NICE reference case. The company did collect the Paediatric Outcomes Data Collection Instrument (PODCI) as a measure of quality of life in VISION-DMD. Outcomes collected in VISION-DMD are further discussed in Section 3.2.2.5.

The company's economic analysis was broadly in line with the NICE reference case. The EAG's major concerns are summarised in the key issues tables, but of note was the use of a blended comparator (prednisone and deflazacort), rather than comparing these are distinct treatment alternatives. This risks obscuring true differences in cost and effect between discrete treatment strategies, and thus could bias estimates of the ICER. The company also included a number of non-reference case costs (e.g., out of pocket costs, transport, and transfer payments) in its base case. The EAG therefore explored the impact of excluding these in the scenario analyses.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Vamorolone for treating Duchenne muscular dystrophy.	Treatment of DMD in patients aged 4 years and older.	The population aged 4 to 7 years of age is supported by VISION-DMD and VBP15-LTE studies presented in B.2.3. Summary of methodology of the relevant clinical effectiveness evidence. The population aged over 7 years of age is supported by an extrapolation report that includes Population Pharmacokinetics and Pharmacokinetics / Pharmacodynamics models as well as an ongoing Phase II Open-Label, Multiple Dose Study (VBP15-006) to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with DMD.	The population addressed in the CS was people with DMD aged 2 years and older. Marketing authorisation was granted for people with DMD aged 4 years and older and the company updated the submission at the clarification stage to reflect this. The children recruited to VISION-DMD were naive to glucocorticoid treatment and were aged 4 to 7 years old. Therefore, they represented the population of children having initial treatment for DMD but do not represent older children who may have had years of treatment with prednisone/prednisolone or deflazacort for DMD.
Intervention	Vamorolone.	Vamorolone.	Not applicable.	The two interventions used in the pivotal trial (VISION-DMD) were vamorolone at 2.0 mg/kg/day and vamorolone at 6.0 mg/kg/day. The EMA granted marketing authorisation for vamorolone up to 6.0 mg/kg/day for DMD.[3]
Comparator(s)	Established clinical management without vamorolone.	Established clinical management without vamorolone i.e., glucocorticoids, as per the clinical pathway of care	Not applicable.	The company interpreted SoC as management with glucocorticoids. Clinical expert advice to the EAG was that the glucocorticoids used for DMD in

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		presented in B.1.3. Health condition and position of the technology in the treatment pathway		the UK were approximately 50% prednisone/prednisolone and 50% deflazacort. The VISION-DMD trial used prednisone as the active comparator. The EAG understood that there were differences in the efficacy and safety profile of prednisone and deflazacort and the EAG was concerned that the pivotal trial did not include a deflazacort comparator arm.
Outcomes	• Walking ability (ambulation) • Muscle function • Muscle strength • Ability to undertake activities of daily living • Bone function • Cardiac function • Concordance and optimisation of treatment • Endocrine function • Lung function • Time to wheelchair • Number of falls • Time to scoliosis • Upper body function • Mortality • Adverse effects of treatment	• Walking ability (ambulation) • Muscle function • Muscle strength • Bone function • Concordance and optimisation of treatment • Adverse effects of treatment • Health-related quality of life (for patients and carers)	Some outcomes were not recorded in the key studies of vamorolone. Both lung function and cardiac function are consequences of muscle function and time to wheelchair can be assessed through walking ability; both are presented as part of the study outcomes. A conservative estimate of equal mortality to steroids has been assumed within the model.	The EAG's clinical experts advised that the function outcomes collected in VISION-DMD represented the standard clinical outcomes used on a day-to-day basis. Clinical expert advice to the EAG was that those outcomes not assessed in the clinical trial were relevant to DMD but would not be expected to occur in the age group and follow-up used in the company's trials. The company did not collect health-related quality of life data using EQ-5D, but did collect the Paediatric Outcomes Data Collection Instrument (PODCI) as a measure of quality of life.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Health-related quality of life (for patients and carers)			
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	A cost-utility analysis was conducted in Excel using the Project HERCULES model framework. QALYs were used to capture the health benefit of treatment and results were presented using the Incremental Cost Effectiveness Ratio (ICER), as appropriate. The time horizon used in the model was 50 years, which was considered long enough to capture the differences in costs and benefits between treatments. Costs were considered from an NHS and PSS perspective. Direct health effects for patients and caregivers were considered. Wider societal costs including productivity losses to the patient and unpaid carers were also considered.	Wider societal costs including productivity losses are important to capture as most DMD patients are cared for on a day-to-day, long-term basis by a combination of formal caregivers (paid), family members and informal caregivers (i.e., non- professional, unpaid). Because the loss of function increases as DMD progresses, the care of DMD patients also increases over time with 24/7 care once patients are on full-time ventilation.	Overall, the EAG considered the company's economic analysis was broadly aligned with the NICE scope. However, a number of out of scope cost items were included in the company's estimate of NHS+PSS costs. The cost associated with diagnostic testing was not included in the company's base case. The company also implemented a blended comparator (prednisone/deflazacort) which may obscure the true incremental cost-effectiveness of vamorolone.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups	Not specified in the scope	Not applicable.	Not applicable.	Not applicable.
Special considerations including issues related to equity or equality	Not specified in the scope	Not applicable.	Not applicable.	Not applicable.

Abbreviations: AESI, Adverse events of special interest; CS, company submission; DMD, Duchenne muscular dystrophy; EAG, External Assessment Group; EMA, European Medicines Agency; EQ-5D, European Quality of Life 5 Dimensions; HERCULES, Health Research Collaboration United in Leading Evidence Synthesis; ICER, Incremental cost-effectiveness ratio; kg, kilograms; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; mg, milligrams; PODCI, Paediatric Outcomes Data Collection Instrument; PSS, Personal Social Services; QALY, quality-adjusted life year; SoC, standard of care.

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify RCTs that have measured the efficacy and safety of treatments for people with Duchenne muscular dystrophy (DMD). A combined literature search strategy was used to identify clinical effectiveness evidence, adverse effects, cost effectiveness evaluations, HRQoL, and cost and resource use data.

The EAG noted some limitations to the searches undertaken for the SLR. The search strategies utilised thesaurus terms to describe interventions rather than free text terms – it is standard practice to use both subject headings combined with free text terms to conduct a comprehensive search. Without free text terms the search may have missed articles not yet indexed, or poorly indexed. The reporting of the searches was also unclear, with timepoints and numbers mismatched between the text and PRISMA diagram. There was also a lack of clarity in how the company searched for and selected studies used to inform parameters in the model (see section 4 for more details). The EAG was not aware of any efficacy studies that were missed in the search, but because of the limitations described, there was a chance that relevant studies were missed. This chance may be greater for studies included in the company's SLR that did not evaluate vamorolone, such as studies used to inform assumptions in the company's economic analysis.

In general, the EAG agreed with the company's principal inclusion criteria for the review: the population was consistent with the marketing authorisation that was subsequently granted for vamorolone and the EAG's clinical expert considered that the interventions/comparators and outcomes were appropriate for this submission. However, the EAG noted that the included study designs were RCTs (followed by single-arm extensions) and single-arm trials despite the protocol also stating that a non-RCT study design was an exclusion criterion. The EAG noted that this led to single-arm studies being both included and excluded from the SLR. Given that non-RCT data was used in the submission via the VBP15-LTE study, the EAG was concerned that other non-RCTs were potentially excluded from the SLR on an ad hoc basis.

The EAG was also unclear about the final studies included in the company's SLR reported clinical effectiveness evidence. The PRISMA diagram presented in Appendix D (Figure 1) indicated that 60 records reporting 49 studies were included in the SLR. For the clinical

effectiveness review, this included 27 papers reporting on 16 trials. The company provided a list of the 60 papers included in the overall SLR, but it was unclear which of the 60 papers were included in the clinical effectiveness review. No details were presented as to the interventions evaluated in the 16 included trials, no results from the trials were presented, and no quality assessment was presented.

The EAG considered that the methods for screening and data extraction were adequate. The tool used for the quality assessment of RCTs was reported to be the CRD's "minimum criteria for assessment of risk of bias in RCTs".[8] Single-arm studies and observational studies were reported to have been quality assessed using the Downs and Black checklist,[9] however, no quality assessment was presented in the SLR (Appendix D).

Table 5: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The company conducted SLRs for each of the research questions listed in the CS. All of the search filters required for each research question were combined into a single search, reported in Appendix D, which covered not only the clinical evidence, but also adverse effects, CEA, HRQoL, and cost and resource use. Published search filters were mostly used (except for the resource use search), and a suitably broad range of sources were searched. Further details of the search are presented in the CS. However, the EAG had concerns over the quality of the searches reported. For example, only thesaurus terms were used to describe the interventions (i.e. no free text terms were used), therefore the search may have missed articles not yet indexed, or poorly indexed. Zero search results are reported for Econlit, but when searched by PenTAG via EBSCOhost there were two relevant articles (although these were picked up via other databases in the company search). Reporting of the search was also unclear at times. For example, while only one search was reported, in the economics section, three searches at different points in time are described: "initial" [2017], "updated" [2019] and then "targeted" [no date reported]. Also, no details were provided of how supplemental searches were executed, and some numbers do not tally between the text and the PRISMA diagram (Figure 1, Appendix D).

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Inclusion criteria	Appendix D, Table 1	The population was consistent with the marketing authorisation that was subsequently granted for vamorolone. The EAG's clinical expert considered the interventions/comparators and outcomes to be appropriate for this submission. The included study designs were RCTs (including single-arm extensions) and single arm trials but the SLR protocol stated that non-RCT study design was an exclusion criteria. The EAG noted that this led to single-arm studies being both included, and excluded, from the SLR. Given data from the dose-finding safety study (VBP15-LTE) was presented in the CS and data from this study used in the economic model, the EAG was concerned that single-arm studies were potentially excluded from the SLR in a non-systematic way.
Screening	Appendix, D1.1	The EAG considered the methods for screening to be adequate.
Data extraction	Appendix, D1.1	The EAG was satisfied with the data extraction process as detailed in Appendix D.
Tool for quality assessment of included study or studies	Appendix, D1.1 and D1.3	The tool used for the quality assessment of RCTs was reported to be the CRD's "minimum criteria for assessment of risk of bias in RCTs".[8] Single-arm studies were reported to have been assessed though the Downs and Black checklist.[9] No quality assessment was presented in the SLR in Appendix D. However, quality assessment of VISION-DMD using CRD's minimum criteria was presented in Section B.2.5 of the CS.
Evidence synthesis	Appendix, D1.1	The PRISMA diagram presented in Appendix D indicated 60 records were included in the SLR. In the clinical review, 27 papers reported on 16 trials were included. Outside of the PRISMA diagram, the company did not present any details of the included clinical studies, including the interventions being tested or the outcomes reported. No evidence synthesis of clinical studies was presented.

Abbreviations: CS, Company submission; CEA, cost-effectiveness analysis; EAG, External Assessment Group; HRQoL, health-related quality of life; PenTAG, Peninsula Technology Assessment Group; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomised controlled trial; SLR, systematic literature review

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

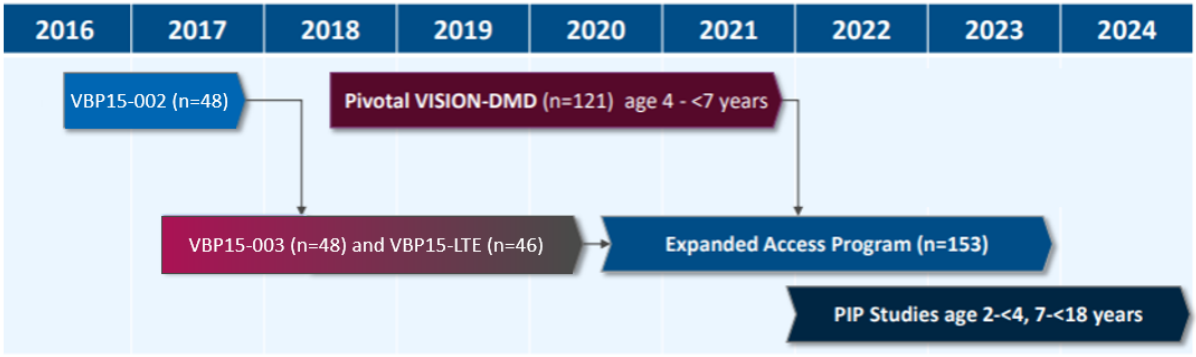
The CS described five Phase II trials of vamorolone:

- VISION-DMD[10,11]
- VBP15-002[12]
- VBP15-003[13]
- VBP15-LTE[14]
- VBP15-006 ("PIP studies")[15]

These are shown in Figure 2, below. The trial in bold was ongoing at the time of the EAG's appraisal. The participants recruited to VBP15-LTE were boys who had previously completed the VBP15-002 and VBP15-003 trials.

As noted previously, the company only presented evidence from VISION-DMD and VBP15-LTE in the CS. Moreover, the evidence presented from VBP15-LTE was limited to a subgroup of participants in the trial. The company presented methodological information about VBP-15-002 and VBP-12-003 trials in the main CS, with summary of results presented in appendices. In Section B.2.11 of the CS, the company noted that VBP15-006[15] was an ongoing, Phase II, open-label, multiple dose study to evaluate vamorolone in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD. This was referred to as "PIP Studies" (paediatric investigational plan) in Figure 2, below. No preliminary results were presented for this trial.

Figure 2: Overview of the vamorolone clinical trial program



Source: CS, Figure 4, Document B

Table 6: Clinical evidence included in the company submission

Study name and acronym	Study design	Phase	Participants enrolled	Population Population	Intervention(s)	Comparator(s)
VISION-DMD[10,11]	Double-blind RCT (24 weeks) followed by treatment extension period (20 weeks)	2b	121	Ambulatory boys aged 4 to <7 years with DMD who were glucocorticoid-naïve at study entry.	• Vamorolone 2.0 mg/kg/day • Vamorolone 6.0 mg/kg/day	• Prednisone 0.75 mg/kg/day • Placebo
VBP15-LTE[14]	Open-label trial (2 years)	2	46[b]	Boys aged 4.5 to 7.5 years with DMD who had completed VBP15-002 (2 weeks) and VBP15-003 (24 weeks) prior to joining VBP15-LTE.	Vamorolone: • 0.25 mg/kg/day • 0.75 mg/kg/day • 2.0 mg/kg/day • 6.0 mg/kg/day A participant's dose could be up-titrated to a maximum of 6.0 mg/kg/day during the trial.	NA

Abbreviations: DMD, Duchenne muscular dystrophy; kg, kilograms; mg, milligrams; NA, not applicable; RCT, Randomised controlled trial.

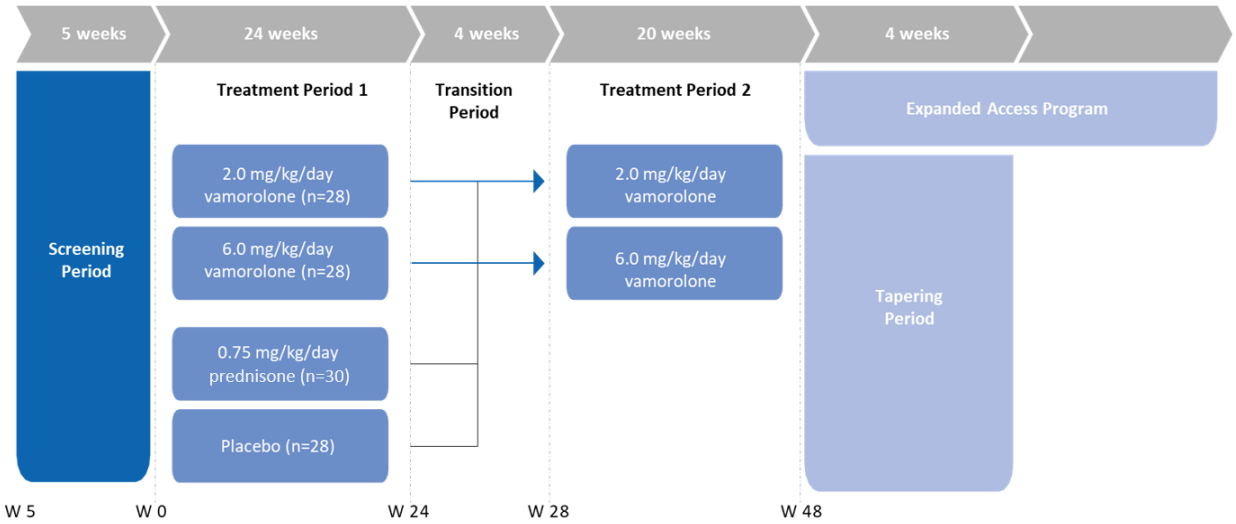
3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The pivotal trial for this submission was **VISION-DMD**,[10,11] a Phase IIb, double-blind, randomised, placebo and active-controlled 48-week trial (Figure 3). The study was undertaken at 33 centres, six of which were in the UK. The EAG was unaware of any rationale to suggest that the trial would have limited generalisability to NHS care. The trial recruited 121 ambulatory boys aged 4 to <7 years with DMD who were glucocorticoid-naïve at study entry.

In treatment period one (24 weeks), participants were randomised 1:1:1:1 to four treatment arms: vamorolone 6.0 mg/kg/day; vamorolone 2.0 mg/kg/day; prednisone 0.75 mg/kg/day; placebo. Following completion of period one, all participants entered a 4-week transition period (i.e., Week 25 to Week 28) during which vamorolone was administered at the same dose as in treatment period one, but the dose of prednisone was tapered to zero. After the transition period, participants then entered treatment period two (20 weeks), during which all participants who were previously treated with either prednisone or placebo were randomised to vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day. Participants who had received vamorolone in treatment period one continued on the vamorolone dose to which they were randomised.

Figure 3: Study design of VISION-DMD



Abbreviations: kg, kilogram; mg, milligram; n, number of participants.
Source: CS, Figure 5, Document B

Trial VBP15-LTE Was the follow-on extension for participants in studies VBP15-002 and VBP15-003. Study **VBP15-002**[12] (NCT02760264) was a Phase IIa, open-label, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys with DMD over a period of two weeks. There were 11 participating international academic clinical recruitment sites, including one site in the UK. Vamorolone was administered to a total of 48 participants at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day. Assignment to dose was not random and the method used was not clear.

Participants who completed VBP15-002 were eligible to join study **VBP15-003**[13] (NCT02760277), which was a Phase II, open-label, multicentre extension study to assess the long term safety and efficacy of vamorolone for DMD over a period of 24 weeks. Forty-eight participants joined the trial and continued on the vamorolone dose assigned at the start of VBP15-002.

Participants who completed VBP15-003 were eligible to join **VBP15-LTE**[14] (NCT03038399), a Phase II study where participants were treated and followed for 24-months. Forty-six participants joined the trial and began the study on the dose assigned at the start of VBP15-002. Their dose was then either escalated to a dose between 2.0 and 6.0 mg/kg/day or maintained between 2.0 and 6.0 mg/kg/day for the trial period. However, the company only reported on the subgroup of 23 participants who were assigned to 2.0 mg/kg/day or 6.0 mg/kg/day in VBP15-002.

3.2.2.2. Population

The population in the final scope issued by NICE was people with DMD and the population addressed in the CS was people with DMD aged 4 years and older. The participants recruited for VISION-DMD and VBP15-LTE were compatible with the scope.

Trial eligibility criteria

Eligibility criteria for VISION-DMD[10,11] were provided in the CS (Document B, Table 9). The trial recruited 121 ambulatory boys aged four to less than seven years old with DMD. This is in line with the EMA Committee for Medicinal Products for Human Use (CHMP) recommendation. The trial included a number of additional eligibility criteria, notably that participants recruited to the trial were required to be ambulatory without assistive devices, able to stand without assistance in less than 10 seconds and weighed between 13 kg and 40 kg at screening. The EAG's clinical

experts explained that children are expected to be ambulatory and able to stand without assistance in less than 10 seconds until they are at least seven years old. Therefore, they would not expect the population of the trial to be biased by these eligibility criteria. The EAG understand that few children would fall outside the weight criteria when aged four to less than seven years old. Participants were required to be glucocorticoid-naïve at study entry, which does not represent the incident population of people with DMD who have typically received one or more glucocorticoids for their DMD. The EAG was uncertain to what extent outcome data from the trials would generalise to positioning after first line (Key Issue 2).

The company did not provide detailed eligibility criteria for VBP15-002[12] in the CS. However, the EAG understood from Conklin et al. (2018)[12] that the criteria for VBP15-002 were a close match to those used for VISION-DMD. VBP15-002 enrolled 48 corticosteroid-naïve participants aged 4 to less than 7 years old with DMD. All 48 participants completed VBP15-002 and joined VBP15-003[13], of whom 46 completed treatment. The 46 participants who completed VBP15-003 joined VBP15-LTE.[14] Therefore, the children who joined VBP15-LTE were boys aged 4.5 to 7.5 years with DMD who had previous been treated with vamorolone for six months.

In sum, children included in VISION-DMD and VBP15-LTE were recently diagnosed with DMD and had either no exposure of glucocorticoids, or in the case of VBP15-LTE, had been treated for 6 months with vamorolone. The EAG understood that this did not include older people with DMD and those who had previously been treated with other glucocorticoids, prednisone/prednisolone or deflazacort, for a period of years. This population was not represented in the vamorolone trials for which results were presented in the CS.

Baseline characteristics

Clinical effectiveness outcomes with vamorolone were reported in the mITT population, who were randomised participants who had at least one dose of study medication and at least one post-baseline efficacy assessment. The demographic characteristics of the mITT population in VISION-DMD were reported in Table 10 in CS Document B. The EAG's clinical experts regarded the participants in VISION-DMD to be generalisable to people in the NHS. They noted that diagnosis in VISION-DMD used a muscle biopsy to look at dystrophy immunofluorescence. At present, diagnosis in the NHS is made on the basis of genetic testing and muscle biopsy is rarely, if ever, required. However, the EAG nevertheless considered that the participants in the trial were representative of NHS clinical practice.

VISION-DMD was a trial with four treatment arms each containing approximately 30 participants. The EAG noted variation between the vamorolone 6.0 mg/kg/day arm and the prednisone arm in four demographic characteristics reported:

- Mean (SD) time to stand from supine (TTSTAND) velocity was 0.19 (0.06) rises per second in the vamorolone 6.0 mg/kg/day arm and 0.22 (0.06) in the prednisone arm. The difference between the two treatment arms was greater than the minimally clinically important difference (MCID; >0.023 rises/sec) for TTSTAND velocity in Table 11 (taken from Table 15, Document B), meaning that those in the vamorolone 6.0 mg/kg/day arm performed poorer on this test at baseline compared to those receiving prednisone.
- The mean (SD) 6-minute walk test (6MWT) distance was 312.5 (56.19) metres in the vamorolone 6.0 mg/kg/day arm and 343.32 (55.84) in the prednisone arm. The difference between the two treatment arms at baseline was greater than the MCID (26-23 metres) in Table 11 (taken from Table 15, Document B), meaning that those in the vamorolone arm performed poorer on this test at baseline compared to those receiving prednisone.
- Time to run/walk 10m (TTRW; SD) velocity was 1.9 (0.4) metres per second in the prednisone arm and 1.6 (0.3/0.4) in the vamorolone arms. The difference between the two treatment arms was greater than the MCID (0.212 m/sec) in Table 11 (taken from Table 15, Document B), meaning that those in the vamorolone arms performed worse on this test at baseline compared to those receiving prednisone.
- North Star Ambulatory Assessment (NSAA; SD) total score was 21.16 (5.45) in the prednisone arm and 18.86 (4.07) in the vamorolone 6.0 mg/kg/day arm. The difference between the two treatment arms was equal to than the MCID (2.32 points) in Table 11 (taken from Table 15, Document B), meaning that those in the vamorolone arms performed worse on this test at baseline compared to those receiving prednisone.

Overall, this suggested that those in the vamorolone 6.0 mg/kg/day arm were likely to have more progressed disease at baseline than the prednisone arm. The EAG's clinical expert confirmed that treatment effectiveness may be reduced as the disease develops, meaning that those with more severe disease at baseline may experience smaller treatment effects in the trial. However, the EAG noted that the TTSTAND, 6MWT, TTRW, and NSAA outcomes were reported (as per standard practice) as a change from baseline and the company used baseline response as a covariate in the mixed model for repeated measures (MMRM) to adjust for

differences at baseline. Given the analysis used, the EAG were not concerned that the variation in baseline characteristics led to an underestimation of the treatment efficacy of vamorolone, but it was noted to be a risk of bias (Section 3.2.2.6).

The EAG requested prior treatments received by participants in VISION-DMD at the clarification stage (Question A7). The prior use of medications appeared well balanced between treatment arms. Three (10.7%) participants in the vamorolone 6 mg/kg/day arm and two (6.5%) participants in the prednisone arm had used glucocorticoids in what the EAG understand to be transient use for no longer than one month.

No baseline characteristics were presented for the participants entering VBP15-002, the majority of whom progressed to VBP15-003 and VBP15-LTE. The company also did not provide the trial clinical study reports (CSRs) with their submission, and so the EAG was unable to identify these independently. The company did present the baseline characteristics of 23 of the 46 participants in VBP15-LTE (Table 12, Document B). These were participants assigned to vamorolone 2.0 or 6 mg/kg/day in VBP15-002/VBP15-003 and maintained at 2 mg/kg/day or more in VBP15-LTE.

Dropouts

The company presented the CONSORT flow diagram for the treatment period one (0-24 weeks) of VISION-DMD in Section D1.2 of the CS. The company detailed the dropouts in treatment period two (24-48 weeks) when assessing the quality of the trial in Table 16 in Section B.2.5 of the CS. Discontinuation in VISION-DMD is summarised below in Table 7. There were low levels of drop out in the trial: one or two participants in each arm discontinued in the initial 24 weeks of the trial (completion rate >90% in each arm), and an additional two participants discontinued in the vamorolone 6 mg/kg/day arm between 24 and 48 weeks (overall completion rate 86.7%). The reasons for discontinuation prior to 24 weeks were provided by the company. The participant in the prednisone arm who discontinued did so due to “personality change”, which may have been related to behaviour issues commonly associated with this treatment. Two participants discontinued vamorolone 6 mg/kg/day at 24 weeks, one due to a refusal to take medication and the other was physician decision due to an eye abnormality. Two participants discontinued placebo due to physician decision and two discontinued vamorolone 2 mg/kg/day due to refusal to take medication and withdrawal to participate in another trial. No details were presented as to why two participants discontinued vamorolone 6 mg/kg/day in the 24 to 48 weeks treatment period.

Table 7: Participant discontinuation by treatment arm in VISION-DMD

	Placebo (n=30)	Prednisone 0.75 mg/kg/day (n=31)	Vamorolone 2 mg/kg/day (n=30)	Vamorolone 6 mg/kg/day (n=30)
Discontinued 0 to 24 weeks	2	1	2	2
Discontinued 24 to 48 weeks	0	0	0	2
Completed study	28	29	28	26

No participants discontinued treatment in the VBP15-002 trial, two participants discontinued during VBP15-003, and five participants discontinued during VBP15-LTE. The company noted in Section B.2.3.4 of the CS that the five withdrawals from VBP15-LTE were for reasons unrelated to the study drug. However, no reasoning for withdrawals was presented for either VBP15-003 or VBP15-LTE and the EAG was unable to critique these discontinuation data.

3.2.2.3. Intervention

In the VISION-DMD trial, vamorolone was administered in a daily dose as an oral suspension, 1.33% weight/weight (wt/wt) in the vamorolone 2.0 mg/kg/day arm and 4.0% wt/wt in the 6.0 mg/kg/day arm. Duration of exposure, in days, to vamorolone was presented in Table 32 of CS Document B (reproduced in Table 8, below). Notably, down-titration for vamorolone from 6.0 mg/kg/day to 4.0 mg/kg/day was not part of the VISION-DMD protocol and the EAG understood that participants used the dose to which they were randomised, outside of dose interruptions or discontinuations due to adverse events, until tapering occurred at the end of the trial. In Section 10.3.1.4. of the VISION-DMD CSR, the company report that 9 subjects had a total of eleven important protocol deviations. These included missed doses and incorrect doses. It was unclear from the reporting what treatment arms these errors occurred in. The EAG was not concerned that these protocol deviations would bias the effect estimates.

Table 8: Summary of 24-week exposure[a] in VISION-DMD

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Median duration of exposure, days (range)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Total exposure (person years)[c]	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Cumulative duration of exposure 20-24 weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: kg, kilograms; mg, milligrams; n, number.

Source: Reproduced from CS, Table 32, Document B

[a] Drug exposure was calculated over the interval for which study drug dispense and return data are available.

[b] Duration of exposure (days) = (date of last dose of study medication – date of first dose of study medication) + 1

[c] Person year = (sum of duration of exposure to treatment (days) over all patients) / 365.25

Permitted and prohibited concomitant medications in VISION-DMD were presented in Table 9 (CS, Document B). The permitted medications included inhaled and/or topical glucocorticoids, providing the dose was stable for the duration of the study, and hydrocortisone (or prednisone) stress dosing was permitted during an illness, injury, or surgical procedure to avoid an adrenal crisis. The EAG's clinical expert did not consider inhaled or topical glucocorticoids were treatments for DMD or that stress dosing with hydrocortisone (or prednisone) would influence the efficacy estimates for vamorolone. The concomitant medications received by participants were well balanced between treatment arms (Clarification Question A8).

With the exception noted above, oral glucocorticoids or other oral immunosuppressive agents, mineralocorticoid receptor agents, idebenone, medications indicated for the treatment of DMD, including Exondys51 and Translarna, were not permitted during the trial.

Interventions trialled in VBP15-002, VBP15-003 and VBP15-LTE were four doses of vamorolone: 0.25 mg/kg/day, 0.75 mg/kg/day, 2 mg/kg/day, and 6 mg/kg/day. Twelve participants were assigned to each dose in VBP15-002, this dose was maintained during VBP15-003. Participants who joined VBP15-LTE started the study on the dose they were assigned in VBP15-002 and participants who started on the 0.25 mg/kg/day or 0.75 mg/kg/day doses were then up-titrated to a dose between 2 mg/kg/day and 6 mg/kg/day until the end of follow-up. Dose de-escalations were allowed in case of intolerability. However, the company did not report the results of the participants in the 0.25 mg/kg/day or 0.75 mg/kg/day arms. The company noted that these participants had more progressed disease at six months before their dose was adjusted to between 2 mg/kg/day and 6 mg/kg/day. The company did not detail the concomitant medications used during the trials. However, the medications permitted and

prohibited during the trials were identical those in the pivotal VISION-DMD trial and the specific concomitant medications used in VISION-DMD were not a cause for concern to the EAG.

3.2.2.4. Comparator

During the first 24 weeks of VISION-DMD, treatment with vamorolone was compared to either prednisone 0.75 mg/kg/day or placebo. Duration of exposure, in days, to prednisone and placebo was presented in Table 32 of Document B and is reproduced in Table 8, above. No other trial phases or studies included a comparator arm to vamorolone. A discussion of background treatments received in the control arm can be found above in the Intervention section (3.2.2.3).

3.2.2.5. Outcomes

For the VISION-DMD trial, the company reported outcomes for all four treatment arms following treatment period one (24-week follow-up). Data after treatment period two (52 weeks) was reported for those who were originally randomised to vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day and those who switched from prednisone or placebo to vamorolone. The company also reported outcomes from the VBP15-LTE at 30 months. The company did not report all of the comparative data in the CS, but the EAG received notable missing data at clarification. For clarity, the treatments assessed in each trial are listed below.

VISION-DMD treatment period 1 (24 weeks):

- Vamorolone 6.0 mg/kg/day for 24 weeks (n=30);
- Vamorolone 2.0 mg/kg/day for 24 weeks (n=30);
- Prednisone 0.75 mg/kg/day for 24 weeks (n=31);
- Placebo for 24 weeks (n=30).

VISION-DMD treatment period 2 (48 weeks):

- Vamorolone 6.0 mg/kg/day for 48 weeks (n=28);
- Vamorolone 2.0 mg/kg/day for 48 weeks (n=38);
- Prednisone 0.75 mg/kg/day for 24 weeks followed by vamorolone 6.0 mg/kg/day for 24 weeks (n=15);

- Prednisone 0.75 mg/kg/day for 24 weeks followed by vamorolone 2.0 mg/kg/day for 24 weeks (n=15);
- Placebo for 24 weeks followed by vamorolone 6.0 mg/kg/day for 24 weeks (n=14);
- Placebo for 24 weeks followed by vamorolone 2.0 mg/kg/day for 24 weeks (n=14).

VBP15-LTE: Change scores reported from the end of VBP15-003, after six months of treatment, until the end of treatment in VBP15-LTE (30 months):

- Vamorolone 2.0 to 6.0 mg/kg/day for 30 months (n=24).

Multiple dose escalations to the highest dose (i.e., 6.0 mg/kg/d) were permitted in the LTE protocol and de-escalations were also allowed in case of intolerability, at the discretion of investigators.

The outcomes assessed in each trial phase and reported in the CS (or during clarification) are shown in Table 9.

Table 9: Clinical effectiveness outcomes from trials of vamorolone reported in the CS

Outcomes listed in the NICE scope	VISION-DMD Phase 1 (24 weeks){Guglieri, 2022 #5}	VISION DMD Phase 1 and 2 (48 weeks){Hoffman, 2023 #7}	VBP15-LTE{Mah, 2022 #11}
Walking ability (ambulation)	✓ 6MWT, TTRW velocity, TTSTAND velocity, TTCLIMB velocity, NSAA score	✓ 6MWT, TTRW velocity, TTSTAND velocity, TTCLIMB velocity, NSAA	✓ 6MWT, TTRW velocity, TTSTAND velocity, TTCLIMB velocity, NSAA, PODCI transfer and basic mobility
Muscle function	✓ As assessed through functional measures, above	✓ As assessed through functional measures, above	✓ As assessed through functional measures, above
Muscle strength	✓ Knee extension and elbow flexor muscle strength	×	×
Ability to undertake activities of daily living	×	×	×

Outcomes listed in the NICE scope	VISION-DMD Phase 1 (24 weeks){Guglieri, 2022 #5}	VISION DMD Phase 1 and 2 (48 weeks){Hoffman, 2023 #7}	VBP15-LTE{Mah, 2022 #11}
Bone function	✓ Height Z-score, lumbar Spine BMD and BMC, and fractures	✓ Height Z-score	✓ Height percentile
Cardiac function	×	×	×
Concordance and optimisation of treatment	×	×	×
Endocrine function	×	×	×
Lung function	×	×	×
Time to wheelchair	×	×	×
Number of falls	×	×	×
Time to scoliosis	×	×	×
Upper body function	×	×	✓ PODCI upper extremity and physical function (n=18)
Mortality	✓	✓	✓
Adverse effects of treatment	✓	✓	✓
Health-related quality of life for patients	× HRQoL was measured using PODCI and PARS III but results were not reported in the CS	×	×
Health-related quality of life for carers	×	×	×
Additional outcomes	✓ TSQM (treatment satisfaction)	×	×

Abbreviations: 6MWT, six-minute walking test; BMC, bone mineral content; BMD, bone mineral density; HRQoL, health-related quality of life; NSAA, North Star Ambulatory Assessment; PARS III, Psychosocial Adjustment and Role Skills Scale III; PODCI, Paediatric Outcomes Data Collection Instrument; TSQM, Treatment Satisfaction Questionnaire; TTCLIMB, Time to climb 4 stairs; TTRW, Time to run/walk 10m; TTSTAND, Time to stand from supine.

Overall, outcome measures reported in the CS were related to participants' ambulatory function and adverse effects of treatment. Measures of ambulatory function reported were widely accepted measures and the company defined thresholds for where change in the outcomes was known to have a clinically meaningful benefit to participants. However, the EAG nevertheless considered there to be an absence of evidence for many of the outcomes in the NICE scope, particularly aspects of the disease other than ambulatory function and outcomes that would

assess the impact of treatments on patient functioning, quality of life, and mental wellbeing. Clinical expert advice to the EAG was that some outcomes, such as cardiac function, lung function, time to scoliosis, time to wheelchair, and number of falls may not be relevant to people with DMD until later in the disease course. As those in VISION-DMD were glucocorticoid-naïve at baseline and follow-up was <12 months, the trial evidence available for vamorolone would be unable to provide an insight into the long term effects of treatment or the effects of treatment for those later in the disease course.

Details of the statistical analysis used for the VISION-DMD trial are reported in Table 14 in Document B. The primary and secondary endpoints were: time to stand from supine (TTSTAND) velocity; time to run or walk 10 metres (TTRW) velocity; time to climb four stairs (TTCLIMB) velocity; North Star Ambulatory Assessment (NSAA) score; knee extension and elbow extension muscle strength. It was notable that NSAA is a 17-item scale that grades performance of various functional skills on a scale from 0 (unable), 1 (completes independently but with modifications), and 2 (completed without compensation). The NSAA score includes, within the 17 items, rise from the floor, climbing on a box, and the ability to walk or run. These items are closely associated with other outcomes collected in the trial such as TTSTAND velocity, TTRW, and TTCLIMB velocity. However, unlike the related outcomes in this trial, it is not scored based on the time taken to complete these tasks and is rather an assessment of how they are performed.

The company conducted two different analyses of primary and secondary outcomes to account for missing data in the trial. The first analysis, conducted for the Food and Drug Administration (FDA), applied a MMRM approach using observed cases (without multiple imputation) and importantly, the MMRM included the baseline response as a covariate. The second analysis, conducted for the European Medicines Agency (EMA), did use multiple imputation using both missing at random (MAR) and missing not at random (MNAR) assumptions. The EMA analysis used Copy-Reference imputation for missing data not related to COVID-19. The primary and secondary endpoints for the vamorolone (either dose) versus prednisone comparisons used the FDA approach. The EAG considered the FDA approach to be more robust as it did not utilise the MAR assumption and used observed cases in the analysis. The EAG noted that population characteristics in VISION-DMD indicated an imbalance in characteristics suggesting that those participants in the vamorolone 6 mg/kg/day arm had more progressed disease, however the company adjusted for this imbalance by including baseline outcome data as a covariate in the MMRM.

Three patient reported outcome measures (PROMs) were collected during VISION-DMD: Paediatric Outcomes Data Collection Instrument (PODCI); Treatment Satisfaction Questionnaire (TSQM); Psychosocial Adjustment and Role Skills Scale III (PARS III). Powell et al. (2020)[16] also assessed PODCI alongside EQ-5D-3L. Powell et al. reported that most instruments, including EQ-5D-3L and PODCI, demonstrated low quality evidence and unsatisfactory or inconsistent validity in DMD, with the majority not featuring direct validation studies in this population. Powell et al. concluded that only KIDSCREEN[17,18] received an adequate rating for instrument design and a satisfactory result for content validity based on its development, yet, like the majority of PROMs, the measure had not been directly validated for use in children with DMD.

The other PROMs collected during VISION-DMD were not measures of a person's QoL. The TSQM is a measure of person's satisfaction with medication. The PARS III instrument was developed to measure psychosocial adjustment in children with chronic physical illnesses. It has been validated for this purpose in the DMD population[19] but does not extend to measure other QoL domains. The EAG did not consider the PROMs collected during VISION-DMD to be adequate measures of quality of life in children with DMD. However, the EAG was not aware of any PROMs designed to measure the quality of life (QoL) of children with DMD.

The statistical analysis used for the outcomes reported from the participants in the VBP15-002, VBP15-003 and VBP15-LTE trials was not detailed in the company submission. However, the appendix to the VBP15-LTE publication stated that the only the observed data was utilised, i.e., no multiple imputation was used.[14]

3.2.2.6. Critical appraisal of the design of the studies

The company stated that quality assessment was undertaken with appropriate checklists on studies included in the SLR. However, no quality assessment was presented in the SLR in Appendix D. In Document B, a quality assessment was presented for the pivotal trial, VISION-DMD. No quality assessment was presented for the VBP15-002/VBP15-003/VBP15-LTE trials of vamorolone.

Quality assessment of VISION-DMD

The company presented a quality assessment of the pivotal trial, VISION-DMD, in Table 16 (Section B.2.5). This assessment was conducted using the "minimum criteria for assessment of risk of bias in RCTs" set out in CRD's guidance for undertaking reviews in health care.[8] The

company undertook the assessment and concluded that VISION-DMD was a high quality study with minimal risk of bias. This has been reproduced in Table 10 with the EAG's critique of the assessment. Overall, the EAG agreed with the company that randomisation appeared to be carried out appropriately, concealment of treatment allocation was adequate, and care providers, participants and outcome assessors were blinded to treatment allocation. However, as noted in Section 3.2.2.2, the treatment arms were quite different at outset in terms of prognostic factors. The vamorolone 6 mg/kg/day arm had lower TTSTAND velocity, 6MWT distance, TTRW velocity, and NSAA total score at baseline than the prednisone arm, indicating more progressed disease. The EAG did not consider this an indication that the allocation sequence was not random, but a consequence of having too few people randomised per arm leading to treatment groups that were noticeably mismatched at baseline.

The EAG understood that there were relevant outcomes collected in the trial that were not presented in the CS. The following outcomes of the key comparison vamorolone 6.0 mg/kg/day versus prednisone at 24 weeks, were not presented in the CS but were provided at the clarification stage: TTRW velocity, NSAA score, knee extension muscle strength, and elbow flexor muscle strength. In Section B.2.6.1.9 the company presented an incomplete summary of the three PROMs collected was at 24 weeks. This summary did not detail the results for the vamorolone 6.0 mg/kg/day versus prednisone comparison.

The company collected efficacy outcomes at 48 weeks across six treatment arms, all of which were using either 6.0 or 2.0 mg/kg/day vamorolone during the 24–48 week treatment period. The outcomes in the prednisone arm who changed to vamorolone treatment were presented only in charts limiting any further analysis by the EAG. Results of the three PROMs were not reported and change in body mass index (BMI) and bone biomarkers were reported in text and this offered an incomplete summary of the results.

Overall, the EAG considered the trial to be at a moderate risk of due to selective reporting of the outcomes collected.

Table 10: EAG critique of the quality assessment of VISION-DMD

Questions	Assessment presented in the CS	EAG's critique
Was randomisation carried out appropriately?	Yes: Patients were randomised 1:1:1:1 ratio by an IXRS after patients were confirmed to have met all study entry criteria, at least 10 days prior to the	The EAG agreed with the company's assessment

Questions	Assessment presented in the CS	EAG's critique
	Baseline Day -1 Visit). Patients were stratified by age at study entry (<6 years and ≥6 years).	
Was the concealment of treatment allocation adequate?	Yes. To maintain the double-blind in this period 1, all patients received either a matching placebo for vamorolone (i.e., a placebo oral suspension), a matching placebo for prednisone (i.e., a placebo tablet) or both (i.e., placebo oral suspension and placebo tablet). Maintenance of the blind was aided by use of amber bottles and acceptability for taste for both the vamorolone and placebo suspensions.	The EAG agreed with the company's assessment
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes: There was no significant difference in the baseline characteristics reported between the treatment arms.	As noted in Section 3.2.2.2, the EAG considered the arms were quite different at outset in terms of baseline characteristics/ prognostic factors. However, MMRM the analysis adjusted for baseline values.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes: Investigators, study site staff, patient's parent/legal guardian, patient, and study monitors were unaware of the treatment assignment throughout the duration of the study.	The EAG agreed with the company's assessment
Were there any unexpected imbalances in dropouts between groups?	No: There were no unexpected imbalances in dropouts between groups. Withdrawals by patients were similar in all arms up to Week 24 (prednisone, n=1; placebo, n=2; vamorolone 2.0 mg/kg/day, n=2; vamorolone 6.0 mg/kg/day, n=2) and up to Week 48 (prednisone, n=1; placebo, n=2; vamorolone 2.0 mg/kg/day, n=2; vamorolone 6.0 mg/kg/day, n=4).	The EAG agreed with the company's assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No: No evidence to suggest that the authors measured more outcomes than they reported.	There were relevant outcomes collected in the trial that were not presented. Four outcomes linked to the vamorolone 6.0 mg/kg/day versus prednisone comparison were presented after a request from

Questions	Assessment presented in the CS	EAG's critique
		the EAG at the clarification stage. Reporting of PROMs collected was incomplete at either 24 or 48 weeks. Outcomes from the prednisone to vamorolone 6.0 mg/kg/day arm at 48 weeks were reported only in charts while results in the vamorolone to vamorolone arms at 48 weeks were provided in tables.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes: Efficacy analysis was performed using the mITT-1 population for efficacy at Week 24 and using the mITT-2 population for efficacy at Week 48. Following the Intent-to-Treat principle, patients were analysed according to the treatments and strata to which they were assigned at randomisation.	The EAG agreed with the company's assessment

Abbreviations: AE, adverse events; EAG, External Assessment Group; IXRS, Interactive voice/web Response System; mITT, modified intention to treat; n, number.

Quality assessment of VBP15-002, VBP15-003, and VBP15-LTE trials

No quality assessment was presented for the VBP15-002,[12] VBP15-003[13], and VBP15-LTE trials.[14] These were consecutive trials where people who completed VBP15-002 were eligible to join VBP15-003, and people who completed VBP15-003 were eligible to join VBP15-LTE. Therefore, the EAG offers a comment on the potential risks of bias pertaining to all three trials.

As open-label, uncontrolled studies, these studies are at an increased risk of bias as it is not possible to determine to what extent changes in the outcomes are due to reasons other than the treatment, and some types of outcomes can be influenced by knowledge of the treatment being received. The trial eligibility criteria of VBP15-002 were closely matched to VISION-DMD and the population was relevant to the appraisal and matched the population in the final scope issued by NICE. However, it was unclear how participants were assigned to treatment arms using vamorolone (at 0.25, 0.75, 2.0, or 6.0 mg/kg/day). Data were only reported in the CS for a subgroup of 23 (50%) of participants in VBP15-LTE who used vamorolone between 2.0 and 6.0 mg/kg/day from the start of VBP15-002.

3.2.3. Description and critique of the results of the studies

In this section, the EAG report the efficacy and safety results submitted by the company from the VISION-DMD TRIAL and the VBP15-LTE study. In this section, the EAG refer to minimal clinically important different (MCID) thresholds reported by the company in Table 15 in Document B and reproduced below in Table 11. The minimum MCID represents the smallest improvement in the outcome that has a meaningful benefit for the person and can represent a standard for determining effectiveness and patient satisfaction with a treatment. The company did not present MCIDs for the exploratory endpoints, knee extension and elbow flexor muscle strength. Within the timeframe of its appraisal, the EAG was unable to validate the MCIDs provided by the company or identify MCIDs for other outcomes.

Table 11: Minimal clinically important different (MCID) thresholds

Endpoint	MCID
TTSTAND velocity	>0.023 rises/sec
6MWT	>26-32 metres
TTRW velocity	>0.212 m/sec
TTCLIMB velocity	>0.035 task/sec
NSAA	>2.32 points

Abbreviations: 6MWT, Six-minute walk test; NSAA, North Star Ambulatory Assessment; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine

Source: adapted from CS, Table 15, Document B

The EAG has divided up the description and critique of the results of the studies into the following three sections:

- VBP15-LTE clinical effectiveness results
- VBP15-LTE clinical effectiveness results : outcomes following 48 weeks of vamorolone and outcomes following 24 weeks of either prednisone or placebo followed by 24 weeks of vamorolone
- VBP15-LTE clinical effectiveness results : outcomes following 30 months of vamorolone at varying doses between 2.0 to 6.0 mg/kg/day

3.2.3.1. VISION-DMD clinical effectiveness results: vamorolone versus prednisone at 24 weeks

A limited selection of efficacy outcome results comparing vamorolone at 6.0 or 2.0 mg/kg/day with prednisone were presented in the CS. The company provided the missing outcome data at the clarification stage (Question A2).

TTSTAND velocity

Participants in all treatment arms, excluding placebo, showed a clinically meaningful improvement in the time taken to stand from supine (TTSTAND) after 24 weeks. Standard errors showed that the treatment effect varied across participants, which is consistent with clinical advice to the EAG that there is variation in response to steroids across people with DMD.

Least squares means (LSM; SE) TTSTAND velocity was numerically faster in the prednisone arm than the vamorolone 2.0 and 6.0 mg/kg/day arms. The effect approached statistical significance as compared with the 2.0 mg/kg/day arm (Table 12). The benefit in the prednisone arm versus the vamorolone 6.0 mg/kg/day arm was close to the MCID for TTSTAND velocity (>0.023 rises/sec). The benefit in the prednisone arm versus the vamorolone 2.0 mg/kg/day arm was greater than the MCID. Vamorolone at either 2.0 or 6.0 mg/kg/day was more efficacious than placebo (effect statistically significant and greater than the MCID).

Overall, the results suggested that vamorolone at either dose offered a meaningful clinical benefit to participants over and above placebo, but that those receiving prednisone were faster to stand than those receiving vamorolone. While this effect was not statistically significant, it matched or exceeded the MCID for this outcome, and the EAG considered that the lack of statistical significance was plausibly related to the sample size and variability in the treatment response across participants in all treatment arms, rather than the absence of an effect.

Table 12: TTSTAND velocity change from baseline to Week 24: vamorolone versus prednisone/placebo

rises/sec	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	0.20 (0.06)	0.22 (0.06)	0.18 (0.05)	0.19 (0.06)
Week 24, mean (SD)	0.19 (0.09)	0.29 (0.09)	0.23 (0.09)	0.24 (0.08)

rises/sec	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Change from baseline at Week 24, mean (SD)	-0.01 (0.06)	0.07 (0.07)	0.04 (0.09)	0.05 (0.07)
LSM (SE) change from baseline	-0.01 (0.01)	0.07 (0.01)	0.03 (0.01)	0.05 (0.01)
LSM difference (SE) vs prednisone	NR	NA	-0.03 (0.02)	-0.02 (0.02)
95% CI vs prednisone	NR	NA	-0.07, 0.00	-0.06, 0.02
p-value vs prednisone	NR	NA	0.0588	0.2976
LSM difference (SE) vs placebo	NA	NR	0.05	0.06 (0.02)
95% CI vs placebo	NA	NR	0.01, 0.08	0.02, 0.10
p-value vs placebo	NA	NR	0.0171	0.002

Abbreviations: CI, confidence interval; kg, kilograms; LSM, least squares mean; mg, milligrams; n, number; NA, not applicable; NR, not reported; SE, standard error.

6MWT distance

Results of the 6-minute walking test (6MWT) showed that participants in all treatment arms, except placebo, showed a clinically meaningful improvement in the outcome after 24 weeks of treatment. As with TTSTAND, measures of variation suggested that the effect was varied across the sample, meaning that some but not all participants may have benefitted from treatment.

LSM (SE) 6MWT distance was numercially better in the prednisone arm than in either of the vamorolone dose arms: during the six minutes, people who received prednisone were able to walk a LSM (SE) of 48.23 (9.12) metres further compared to 28.34 (9.56) metres and 23.88 (9.69) metres in the vamorolone at 6.0 or 2.0 mg/kg/day arms respectively. However, the difference did not exceed the MCID (>26-32 metres), meaning that the relative improvement after predinisone would not have an overall meaningful impact on participants' lives (Table 11). Vamorolone at either 2.0 or 6.0 mg/kg/day was more efficacious than placebo (effect statistically significant and greater than the MCID).

Table 13: 6MWT distance change from baseline to Week 24: vamorolone versus prednisone/placebo

metres	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	354.5 (77.59)	343.3 (55.84)	316.1 (58.43)	312.5 (56.19)
Week 24, mean (SD)	339.0 (60.90)	395.5 (57.32)	349.1 (65.99)	355.9 (50.92)
Change from baseline at Week 24, mean (SD)	-23.9 (59.62)	39.7 (30.620	31.0 (51.12)	28.8 (49.66)
LSM (SE) change from baseline	-13.25 (10.04)	48.23 (9.12)	23.88 (9.69)	28.34 (9.56)
LSM difference (SE) vs prednisone	NR	NA	-24.35 (13.21)	-19.89 (13.10)
95% CI vs prednisone	NR	NA	-50.61, 1.91	-45.93, 6.15
p-value vs prednisone	NR	NA	0.0687	0.1326
LSM difference (SE) vs placebo	NA	NR	37.12 (13.87)	41.59 (13.76)
95% CI vs placebo	NA	NR	9.55, 64.70	14.23, 68.94
p-value vs placebo	NA	NR	0.0089	0.0033

Abbreviations: CI, confidence interval; kg, kilograms; LSM, least squares mean; mg, milligrams; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

TTRW velocity

Participants in the prednisone and vamorolone 6.0mg/kg/day arms showed an improvement in the time needed to run/walk 10 metres (TTRW) after 24 weeks' of treatment, but those in the vamorolone 2.0 mg/kg/day and placebo arms did not. As with previous outcomes, measures of variability indicated that the response varied across participants.

LSM (SE) TTRW velocity was numerically faster in the prednisone arm than the vamorolone 6.0 mg/kg/day arm and statistically significantly faster than the vamorolone 2.0 mg/kg/day arm (Table 14). The LSM (SE) velocity in the prednisone arm improved by 0.37 (0.05) metres per second (m/sec) compared to 0.26 (0.05) m/sec and 0.14 (0.06) m/sec in the vamorolone at 6.0 or 2.0 mg/kg/day arms respectively. The benefit in the prednisone arm versus the vamorolone

2.0 mg/kg/day arm was greater than the MCID (>0.212 m/sec). The benefit of vamorolone 6.0 mg/kg/day over placebo was both statistically significant and greater than the MCID.

Overall, the results showed that prednisone was more effective than vamorolone 2.0 mg/kg/day but not meaningfully different than vamorolone 6.0 mg/kg/day. Vamorolone was more effiective than placebo at a dose of 6.0 g/kg/day but not at 2.0 mg/kg/day.

Table 14: TTRW velocity change from baseline to Week 24: vamorolone versus prednisone/placebo

metres/sec	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	1.74 (0.35)	1.90 (0.43)	1.56 (0.29)	1.60 (0.36)
Week 24, mean (SD)	1.77 (0.44)	2.25 (0.43)	1.72 (0.37)	1.89 (0.41)
Change from baseline at Week 24, mean (SD)	0.02 (0.33)	0.34 (0.24)	0.16 (0.23)	0.28 (0.28)
LSM (SE) change from baseline	0.01 (0.06)	0.37 (0.05)	0.14 (0.06)	0.26 (0.05)
LSM difference (SE) vs prednisone	NR	NA	-0.23 (0.08)	-0.11 (0.08)
95% CI vs prednisone	NR	NA	-0.38, -0.08	-0.26, 0.04
p-value vs prednisone	NR	NA	0.0036	0.1381
LSM difference (SE) vs placebo	NA	NR	0.13 (0.08)	0.24 (0.08)
95% CI vs placebo	NA	NR	-0.03, 0.28	0.09, 0.39
p-value vs placebo	NA	NR	0.10	0.00

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

TTCLIMB velocity

Results showed that participants in all treatment arms, except placebo, had a clinically meaningful improvement in the time needed to climb four stairs (TTCLIMB) after 24 weeks of treatment.

LSM (SE) TTCLIMB velocity was statistically significantly faster in the prednisone arm than in either of the vamorolone arms (Table 15). In the prednisone arm, velocity increased by 0.11 (0.10) steps per second (step/sec) compared to 0.06 (0.01) step/sec and 0.05 (0.08) step/sec in the vamorolone arm at 6.0 or 2.0 mg/kg/day arms, respectively. In both cases the benefit in the prednisone arm over the vamorolone dose arms was greater than the MCID (>0.035 task/sec) reported in Table 11.

Overall, prednisone was more effective than vamorolone at either 2.0 or 6.0 mg/kg/day. Vamorolone was more efficacious than placebo at either dose (effect statistically significant and greater than the MCID).

Table 15: TTCLIMB velocity change from baseline to Week 24: vamorolone versus prednisone/placebo

step/sec	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	0.25 (0.09)	0.29 (0.11)	0.20 (0.05)	0.21 (0.09)
Week 24, mean (SD)	0.25 (0.12)	0.41 (0.16)	0.26 (0.08)	0.27 (0.10)
Change from baseline at Week 24, mean (SD)	-0.01 (0.05)	0.11 (0.10)	0.06 (0.06)	0.07 (0.06)
LSM (SE) change from baseline	-0.01 (0.02)	0.11 (0.01)	0.05 (0.02)	0.06 (0.01)
LSM difference (SE) vs prednisone	NR	NA	-0.06 (0.02)	-0.05 (0.02)
95% CI vs prednisone	NR	NA	-0.10, -0.02	-0.09, -0.01
p-value vs prednisone	NR	NA	0.0057	0.0193
LSM difference (SE) vs placebo	NA	NR	0.06 (0.02)	0.07 (0.02)
95% CI vs placebo	NA	NR	0.02, 0.1	0.03, 0.11
p-value vs placebo	NA	NR	0.0056	0.0008

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

NSAA score

Results showed that participants in all treatment arms, except placebo, showed a clinically meaningful improvement in functional skills as assessed by the NSAA scale after 24 weeks of treatment. People receive a score between 0 to 34, where a higher score is considered better. Measures of variability suggested some variation in response across participants. LSM (SE) NSAA score was numercially higher in the prednisone arm than in either of the vamorolone dose arms (Table 16). The LSM (SE) change from baseline was 4.5 (3.66) points in the prednisone arm compared to 2.85 (0.61) points and 2.52 (0.86) step/sec in the vamorolone at 6.0 or 2.0 mg/kg/day arms respectively. In neither case was the benefit in the prednisone arm over the vamorolome arms greater than the MCID (>2.32 points) reported in Table 11.

Overall, prednisone had a numerical but not a clinically meaninful benefit over vamorolone at either dose. Vamorolone was more efficacious than placebo at either dose (effect statistically significant and greater than the MCID).

Table 16: NSAA score[a] change from baseline to Week 24: vamorolone versus prednisone

	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline, mean (SD)	18.9 (5.30)	21.2 (5.45)	17.2 (4.66)	18.9 (4.07)
Week 24, mean (SD)	18.9 (5.60)	25.6 (5.47)	20.4 (5.62)	22.0 (5.17)
Change from baseline at Week 24, mean (SD)	-0.2 (2.57)	4.5 (3.66)	3.0 (3.11)	3.2 (3.18)
LSM (SE) change from baseline	-0.73 (0.62)	4.29 (0.60)	2.52 (0.63)	2.85 (0.61)
LSM difference (SE) vs prednisone	NR	NA	-1.76 (0.86)	-1.44 (0.83)
95% CI vs prednisone	NR	NA	-3.48, -0.05	-3.09, 0.20
p-value vs prednisone	NR	NA	0.0437	0.0848
LSM difference (SE) vs placebo	NA	NR	3.25 (0.87)	3.57 (0.84)
95% CI vs placebo	NA	NR	1.53, 4.97	1.90, 5.25
p-value vs placebo	NA	NR	0.0003	<0.0001

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

Note: [a] Range of scores is 0-34. Higher is better.

Knee extension and elbow flexor muscle strength

Participants in all arms, including those receiving placebo, showed an improvement in knee extension muscle strength after 24 weeks of treatment. As noted previously, the EAG were not aware of a MCID for this outcome to determine whether these differences would have been clinically meaningful for participants. Measures of variation suggested that there was variability in response across participants.

LSM (SE) knee extension muscle strength was numerically greater in the prednisone arm than the vamorolone 6.0 mg/kg/day arm, and statistically significantly greater than the vamorolone 2.0 mg/kg/day arm (Table 17). Vamorolone at either 2.0 or 6.0 mg/kg/day offered a numerical benefit over placebo.

Table 17: Knee extension muscle strength change from baseline to Week 24: vamorolone versus prednisone

	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline (kg), mean (SD)	5.57 (2.04)	6.13 (1.41)	5.30 (1.81)	5.47 (1.74)
Week 24, mean (SD)	5.64 (2.37)	6.89 (1.86)	5.37 (2.15)	5.52 (2.22)
Change from baseline at Week 24, mean (SD)	0.15 (2.10)	0.85 (1.57)	0.12 (1.32)	0.28 (1.93)
LSM (SE) change from baseline	-0.06 (0.36)	1.01 (0.34)	0.00 (0.38)	0.01 (0.36)
LSM difference (SE) vs prednisone	NR	NA	-1.01 (0.50)	-0.91 (0.48)
95% CI vs prednisone	NR	NA	-2.00, -0.02	-1.87, 0.05
p-value vs prednisone	NR	NA	0.0456	0.0617
LSM difference (SE) vs placebo	NA	NR	0.07 (0.51)	0.16 (0.49)
95% CI vs placebo	NA	NR	-0.95, 1.08	-0.82, 1.14
p-value vs placebo	NA	NR	0.8987	0.7411

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

Participants in all treatment arms, except placebo, showed an imrpovement in muscle strength after 24 weeks of treatment. The EAG did not have a MCID for this outcome to appraise whether this change would have been clinically meaningful to participants. Measures of variation suggested that there was variability in treatment response across participants.

Counterintuitively, elbow flexor muscle strength improved more (numerically) following the lower 2.0 mg/kg/day dose of vamorolone than the 6.0 mg/kg/day dose. LSM (SE) elbow flexor muscle strength was statistically significantly greater in the prednisone arm than the vamorolone 6.0 mg/kg/day arm, and the prednisone arm was numerically greater than the vamorolone 2.0 mg/kg/day arm (Table 18).

Overall, prednisone was the most effective treatment for elbow muscle strength, though vamorolone showed some benefits over placebo.

Table 18: Elbow flexor muscle strength change from baseline to Week 24: vamorolone versus prednisone

	Placebo (n=28)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
Baseline (kg), mean (SD)	3.38 (1.49)	3.27 (0.94)	2.68 (0.81)	2.86 (0.78)
Week 24, mean (SD)	3.26 (1.33)	4.11 (0.98)	3.48 (0.94)	3.34 (1.13)
Change from baseline at Week 24, mean (SD)	-0.15 (1.41)	0.86 (0.78)	0.74 (1.23)	0.50 (1.16)
LSM (SE) change from baseline	0.02 (0.21)	1.05 (0.19)	0.61 (0.22)	0.43 (0.20)
LSM difference (SE) vs prednisone	NR	NA	-0.44 (0.29)	-0.61 (0.27)
95% CI vs prednisone	NR	NA	-1.02, 0.14	-1.16, -0.07
p-value vs prednisone	NR	NA	0.1353	0.0269
LSM difference (SE) vs placebo	NA	NR	0.59 (0.30)	0.41 (0.28)
95% CI vs placebo	NA	NR	-0.01, 1.19	-0.15, 0.98
p-value vs placebo	NA	NR	0.0546	0.1485

Abbreviations: CI, confidence interval; kg, kilogram; LSM, Least squares mean; mg, milligram; n, number; NA, not applicable; NR, not reported; SD, standard deviation; SE, standard error.

Health-related quality of life/ patient reported outcomes

The company did not report the results from the PROMs assessed during the trial (PODCI, PARS III and TSQM). In Section B.2.6.1.9 of the CS, the company stated that results for both the PODCI and the TSQM showed no statistically significant differences between either vamorolone doses and placebo, and vamorolone 2.0 mg/kg/day showed better adjustment for anxiety and depression compared with prednisone as assessed by PARS III. The EAG assumed that no treatment benefit as assessed using PARS III was identified for the higher dose of vamorolone as compared to other treatment arms. As the company did not present these data, the EAG was unable to appraise the reliability of the company's statements.

Subgroup analyses

At clarification (Question A6), the company provided subgroup analyses to compare the treatment effect of vamorolone 6.0 mg/kg/day versus prednisone on the TTSTAND velocity outcome across different population subgroups. A forest plot of subgroup treatment effects has been reproduced in Figure 4, below.

Overall, relative treatment effects between vamorolone and prednisone were fairly consistent across subgroups tested. In all cases, however, 95% confidence intervals were wide, suggesting that there is uncertainty in all treatment effects. This was not surprising, given the small sample size of the trial meaning that subgroup analyses may be underpowered. There was some evidence that the treatment effect may vary according to participants ethnicity and age, but the EAG was not confident in these findings given the uncertainty in treatment effects.

In addition, the company presented subgroup analysis for the vamorolone 6.0 mg/kg/day versus placebo comparison using the TTSTAND velocity outcome in Figure 17 in Section B.2.7 of the CS. This indicated a consistent benefit of vamorolone 6.0 mg/kg/day over placebo across the subgroup categories.

Figure 4: Forest plot TTSTAND velocity in subgroups: vamorolone 6 mg/kg/day versus prednisone

Abbreviations: 6MWT, Six-minute walk test; BL, baseline; kg, kilograms; mg, milligrams; mITT, modified intention to treat; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine.

3.2.3.2. VISION-DMD clinical effectiveness results at 48 weeks

In Section B.2.6.2, the company presented four selected efficacy outcomes in VISION-DMD participants who had received 48 weeks of treatment with vamorolone. The company also presented some efficacy data in participants who had 24 weeks of treatment with prednisone followed by 24 weeks of treatment with vamorolone 6.0 mg/kg/day.

48-week treatment with vamorolone

Improvements in TTSTAND velocity, 6MWT distance, TTRW velocity, and NSAA score demonstrated at 24 weeks in participants treated with vamorolone were largely maintained after 48 weeks of treatment (Table 19). There was no consistent evidence of an improvement or decline in treatment effect in the vamorolone 6.0 mg/kg/day arm, though there was a trend for a decline in the treatment effect in those treated with 2.0 mg/kg/day. Most differences in the 2.0 mg/kg/day arm were slight, though the clinically meaningful benefit in TTSTAND velocity at 24 weeks had disappeared by 48 weeks. Given the known variability around treatment outcomes with glucocorticoids, the small sample size, and uncertainties in the rate of disease progression in DMD, the EAG was unable to determine if the trend for outcomes to reduce after 24 weeks in the 2.0 mg/kg/day arm were due only to chance or whether there was evidence of treatment waning. However, the EAG did consider the evidence to suggest that there was no evidence of a continued improvement in outcomes after 24 weeks of treatment.

Table 19: Change from baseline at Week 24 and Week 48

	Vamorolone 2.0 mg/kg/day (n=30)	**Vamorolone 6.0 mg/kg/day (n=28 at week 24 and n=26 at week 48)**
TTSTAND velocity (rises/sec)		
LSM (SE) change from baseline at week 24	[redacted]	[redacted]
LSM (SE) change from baseline at week 48	[redacted]	[redacted]
6MWT distance (metres)		
LSM (SE) change from baseline at week 24	[redacted]	[redacted]
LSM (SE) change from baseline at week 48	[redacted]	[redacted]
TTRW velocity (metres/sec)		

	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28 at week 24 and n=26 at week 48)
LSM (SE) change from baseline at week 24	[redacted]	[redacted]
LSM (SE) change from baseline at week 48	[redacted]	[redacted]
NSAA score (0-34)		
LSM (SE) change from baseline at week 24	[redacted]	[redacted]
LSM (SE) change from baseline at week 48	[redacted]	[redacted]

Abbreviations: 6MWT, Six-minute walk test; kg, kilogram; LSM, least squares mean; mg, milligram; n, number; NSAA, North Star Ambulatory Assessment; SE, Standard error; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine.

Switch from prednisone to vamorolone

In Section B.2.6.2.5. of the CS, the company presented a comparison of the 28 participants who were randomised to vamorolone 6.0 mg/kg/day for 48 weeks to 15 participants who were randomised to prednisone for 24 weeks followed by vamorolone 6.0 mg/kg/day for 24 weeks. These data were presented as line graphs only, without the accompanying data points, and therefore the findings lacked precision for appraisal. These charts were presented in Doc B of the CS, figures 12 – 15.

The company claimed that the charts demonstrated that [redacted] after participants were switched to vamorolone 6.0 mg/kg/day. In general, outcomes for both arms (vamorolone-vamorolone and prednisone-vamorolone) [redacted] was noticeable for those switching from prednisone to vamorolone, though error bars around the effects were wide and overlapping (presumably leading to the company's conclusion of no reduction in effect). The EAG disagreed with the company somewhat – while it concluded that there was no clear evidence that treatment outcomes reduced after switching from prednisone to vamorolone, the evidence nevertheless suggested that this was possible. Given evidence that prednisone may outperform vamorolone for clinical outcomes, the EAG considered it plausible that longer follow-up data would show a reduction in treatment effect following a switch from prednisone to vamorolone 6.0 mg/kg/day.

As the company did not report data points for these outcomes, the EAG was also unable to appraise whether the effect of vamorolone following receipt of prednisone was consistent with the treatment effect when participants were steroid naïve. The effect of sequencing on treatment effects is a remaining uncertainty in this appraisal (Key Issue 2).

3.2.3.3. VBP15-LTE clinical effectiveness results

The company reported efficacy data from the VBP15-LTE trial in Table 31 in Section B.2.6.3 of the CS. The company stated that participants initiated on the higher doses of vamorolone (those evaluated in VISION-DMD; 2.0 and 6.0 mg/kg/day) had better clinical outcomes after 6 months' of treatment compared with those initially treated with lower doses (0.25 or 0.75 mg/kg/day). No data were presented for the lower dose treatment arms, and all data in the CS from VBP15-LTE were for the higher dose arms. Mah et al. (2022)[14] provided a more complete view of the VBP15-LTE results and the EAG present these in an adapted table below (Table 20) showing the difference between outcomes after 6 and 30 months' of treatment.

Broadly speaking, results after 6 months of treatment at the start of VBP-LTE were comparable with those reported in VISION-DMD. The results showed a reduction in TTSTAND velocity between 6 and 24 months, though overall outcomes appeared to be stable.

Table 20: Summary of efficacy outcomes from VBP15-LTE in participants who maintained a vamorolone dose at 2.0 mg/kg/day or more

Parameter	Mean (SD) after 6 months' treatment	Mean (SD) after 30 months' treatment
TTSTAND velocity in rises/sec (n=23)	0.25 (0.10)	0.20 (0.13)
TTCLIMB velocity in tasks/sec (n=23)	0.31 (0.13)	0.32 (0.19)
TTRW velocity in metres/sec (n=23)	1.90 (0.34)	1.87 (0.63)
6MWT in metres walked (n=20)	377.9 (64.77)	369.9 (77.81)
NSAA score (n=23)	22.3 (4.72)	21.78 (7.86)
Height percentile (n=23)	32.26 (26.87)	37.03 (31.14)
BMI z score	1.28 (0.51)	1.52 (0.66)
PODCI upper extremity and physical function (n=18)	75.34 (15.09)	82.32 (10.91)
PODCI transfer and basic mobility (n=19)	86.55 (9.21)	81.44 (17.54)

Abbreviations: 6MWT, Six-minute walk test; BMI, Body Mass Index; n, number; NSAA, North Star Ambulatory Assessment; PODCI, Paediatric Outcomes Data Collection Instrument; SD, Standard deviation; TTCLIMB, Time to climb four stairs; TTRW, Time to run or walk 10 metres; TTSTAND, Time to stand from supine

Source: Mah et al. (2022)[14]

3.2.3.4. Adverse effects

In this section we present an overview of the evidence for treatment-emergent adverse events (TEAEs) and selected adverse events that are common adverse effects of glucocorticoid treatments in people with DMD.

Treatment-emergent adverse events

The company reported TEAEs in participants in the treatment and comparator arms at 24 weeks in Table 33 and Table 34 in Section B.2.10.1.2 of the CS. The number of participants experiencing TEAEs were similar across all four treatment arms (range 79.3% to 89.3%). A [redacted] in the vamorolone dose arms and prednisone arm had TEAEs leading to dose interruption. There was [redacted] reported in the prednisone arm and [redacted] in the vamorolone 2.0 mg/kg/day arm. One TEAE led to [redacted] and one led [redacted], both in the [redacted], but [redacted] in any of the treatment arms.

Overall, there were no meaningful differences in TEAE between prednisone and vamorolone after 24 weeks of treatment. TEAEs were only slightly increased for vamorolone and prednisone as compared to placebo, though there may be a small increased risk of serious and severe TEAEs

Table 21: Summary of TEAEs at 24 weeks

	Placebo (n=29)	**Prednisone (n=31)**	**Vamorolone 2.0 mg/kg/day (n=30)**	**Vamorolone 6.0 mg/kg/day (n=28)**
TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
TEAEs leading to dose interruption (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to withdrawal from treatment (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to withdrawal from study (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to death (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: kg, kilogram; mg, milligram; n, number; TEAE, treatment emergent adverse events.

Source: CS, reproduced from Table 33, Document B

AEs at week 48 of VISION-DMD were briefly summarised in Section B.2.10.2 of the CS. The company noted that no deaths occurred during the trial but three serious adverse events, all in the vamorolone 6.0 mg/kg/day arm, occurred between week 24 and week 48 of the trial. These events were perforated appendicitis, asthma, and viral gastroenteritis, and were all considered unrelated to treatment with vamorolone.

A summary of AEs experienced by participants during VBP15-LTE was presented in Section B.2.10.3. of the CS and has been reproduced in **Error! Reference source not found.**, below. These data were based on participants receiving varying doses between 2.0 and 6.0 mg/kg/day. The company stated that there were two serious TEAEs: moderate pneumonia in one participant and severe myoglobinuria, which occurred twice in one participant. One participant withdrew from the study due to moderate muscle weakness. The company noted that 10 participants (24.4%) treated with vamorolone at 6.0 mg/kg/day deescalated to 2.0 mg/kg/day owing to a TEAE of weight gain, and that weight gain abated among six participants after dose reduction.

Table 22: Summary of TEAEs, VBP15-LTE

	0.25 mg/kg/day (n=11)	0.75 mg/kg/day (n=23)	2.0 mg/kg/day (n=38)	4.0 mg/kg/day (n=3)	6.0 mg/kg/day (n=41)
Any TEAE, n (%)	4 (36.4)	14 (60.9)	29 (76.3)	1 (33.3)	39 (95.1)

	0.25 mg/kg/day (n=11)	**0.75 mg/kg/day (n=23)**	**2.0 mg/kg/day (n=38)**	**4.0 mg/kg/day (n=3)**	**6.0 mg/kg/day (n=41)**
Any Treatment-related TEAE	0	0	8 (21.1)	1 (33.3)	23 (56.1)
Any TEAE with CTCAE Grade ≥ 3	0	1 (4.3)	0	0	1 (2.4)
Any TEAE Leading to Discontinuation of Study	0	0	1 (2.6)	0	0
Any SAE	0	1 (4.3)	0	0	1 (2.4)
Any Serious TEAE	0	1 (4.3)	0	0	1 (2.4)

Abbreviations: AE, adverse events; CTCAE, Common Terminology Criteria for AEs; n, number; TEAE, treatment-emergent adverse events

Source: Company Submission, Document B, Table 38

Behavioural outcomes

After 24 weeks, there was an increased risk of behavioural problems with prednisone compared to all other treatment options. The severity of these behaviour problems was unclear, but the company noted that [redacted] in the [redacted] [redacted] the study because of [redacted] and one participant displayed aggression characterised as severe (CTCAE grade 2) who remained in the trial. At 48 weeks, there was a reduction in the number of people experiencing behavioural problems following treatment with vamorolone. Behavioural outcomes were not reported for VBP15-LTE.

Weight gain

Weight gain can be an adverse effect of treatment with glucocorticoids. After 24 weeks of treatment, there was an increased risk of weight gain following vamorolone 6.0 mg/kg/day as compared to prednisone or placebo, though event rates were small. In the trial CSR, the company reported that [redacted].

Table 23: Adverse events of special interest

	Placebo (n=29)	Prednisone (n=31)	Vamorolone 2.0 mg/kg/day (n=30)	Vamorolone 6.0 mg/kg/day (n=28)
At least 1 clinically relevant AE	[redacted]	[redacted]	[redacted]	[redacted]
Behaviour problems	[redacted]	[redacted]	[redacted]	[redacted]
Cataracts and glaucoma	[redacted]	[redacted]	[redacted]	[redacted]
Cushingoid features	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Infections	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal disorder	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic conditions	[redacted]	[redacted]	[redacted]	[redacted]
Skin/hair changes	[redacted]	[redacted]	[redacted]	[redacted]
Weight gain	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse events; kg, kilogram; mg, milligram; n, number; TEAE, treatment emergent adverse events.

Source: CS, reproduced from Table 36, Document B

Stunted growth

Stunted growth may occur naturally in those with DMD and may be exacerbated with the use of steroid treatment. At clarification (Question A9), the company reported the change from baseline in height Z-score at 24 weeks. Z-scores for height were calculated in comparison with age- and sex-standardised growth charts for the USA,[10,20] and the z-scores therefore represent the comparability of participants' height with those in a non-DMD population. Positive z-scores represent a better outcome than the cohort, while negative z-scores represent a poorer outcome.

[redacted]

(Table 24).

Table 24: Height Z-score change from baseline to Week 24

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

Abbreviations: CI, Confidence interval; kg, kilogram; LSM – least squares mean; mg, milligram; n, number; SD, standard deviation; SE, standard error.

Source: reproduced from Table 9 in the clarification response

However, the company presented figures to suggest that after 48 weeks' of treatment, participants receiving [redacted] (see **Error! Reference source not found.**). The EAG noted that changes in height z-score at 48 weeks were small, though agreed with the company that [redacted] in participants receiving vamorolone in the trial. Clinical expert advice to the EAG was that even small benefits in height at this length of follow-up may be meaningful if they represent a trend away from growth stunting. However, the EAG considered that further follow-up data would be needed to determine if these data represent a trend for this outcome.

Figure 5: Height Z-score changes from period 1 prednisone switch to vamorolone

Source: CS, Figure 20, Document B

Bone health and fractures

In Section B.2.10.2.2, the company reported the results of bone health outcomes at 24 weeks as assessed using lumbar spine bone mineral content (BMC) and bone mineral density (BMD). The bone health through lumbar spine and total body BMC and BMD was reported in the VISION-DMD clinical study report (CSR)[21] and adapted for this report in Table 25.

The results showed a [redacted] in percent change from baseline in lumbar spine BMD and lumbar spine BMC. However, the EAG considered that this should be interpreted with caution due to missing data at baseline and at 24 weeks. The EAG was unclear how to interpret changes in lumbar spine BMD and BMC outcomes and was unable to obtain clinical expert views on this issue within the timeframe of the appraisal. However, the EAG noted that lower lumbar spine BMD and BMC was a risk factor for vertebral fracture.

Table 25: Percent Change from Baseline to Week 24 in Lumbar Spine BMD and BMC

	Placebo (n=29)	**Prednisone 0.75 mg/kg (n=31)**	**Vamorolone 2.0 mg/kg (n=30)**	**Vamorolone 6.0 mg/kg (n=28)**
Lumbar spine BMD (L1-L4), g/cm^2				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo (n=29)	Prednisone 0.75 mg/kg (n=31)	Vamorolone 2.0 mg/kg (n=30)	Vamorolone 6.0 mg/kg (n=28)
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Percent Change from Baseline at 24 weeks				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Lumbar spine BMC (L1-L4), g				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Percent Change from Baseline at 24 weeks				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMC, Bone mineral content; BMD, Bone mineral density; n, number; SD, standard deviation

In Section B.2.10.1.2 of the CS, the company reported on treatment-emergent vertebral fractures during 24-week trial treatment period one in VISION-DMD. No vertebral fractures occurred in either vamorolone arm, one fracture occurred in the placebo arm, and one fracture in the prednisone arm. Given the small number of events in this data set, the EAG considered that this result could have occurred by chance and so further evidence is needed to determine any effect for this outcome. The EAG's clinical experts warned that benefits and harms in bone and growth-related outcomes may occur over a longer time period than 24 weeks.

The company used the fracture data from VBP15-LTE as an input in the economic model. At 30-months follow-up, six participants (13.0%) were observed to have a total of seven clinical fracture events according to local site adverse event reporting, including one participant with a vertebral fracture and a foot fracture on two separate occasions, three participants with an upper limb fracture, one participant with a vertebral compression fracture, and one participant with multiple vertebral fractures. The EAGs clinical experts noted that vertebral fractures are a known adverse event linked to steroid treatment and these do not occur in those who are untreated. However, limb fractures occur in both untreated and treated people with DMD. The company did not detail the treatments arms of the people who sustained fractures and it was unclear if the fractures are linked to the dose of vamorolone participants were using.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In Section B.2.9 of the CS, the company stated that no formal indirect treatment comparison was conducted as the VISION-DMD study captured all clinical evidence of interest. However, a post-hoc, cross-study, indirect comparison, was conducted to compare vamorolone with prednisone and deflazacort. This comparison used data from VISION-DMD[10,11], VBP15-LTE and the FOR-DMD[14] trial, which compared different regiments of prednisone and deflazacort. The aim of the company's analysis was to compare treatment arms over a longer duration than the 24-week head-to-head comparison available from VISION-DMD.

The FOR-DMD trial[4] was a double-blind, Phase III, RCT to evaluate different glucocorticoid regimens in 196 ambulatory boys aged 4 to <7 years with DMD who were glucocorticoid-naïve at study entry. The study randomised participants to daily dosing of deflazacort, daily dosing of prednisone, or intermittent dosing of prednisone. The company also noted that the FOR-DMD Co-Study Chair, Dr Michela Guglieri, was also Study Chair for VISION-DMD and the two trials used similar methods, including comparable outcome measures, overlapping recruitment sites, similar treatment regimens (same prednisone and placebo tablets used for both studies; same treatment bands for prednisone dose), an overlap of treatment duration (48-week assessment); and similar study populations. The EAG considered that given the similarity in methods, including populations recruited, outcome measures collected, and recruitment sites, the studies were sufficiently similar to compare to one another.

The indirect comparison compared prednisone 0.75 mg/kg/day (n=55) or deflazacort 0.9 mg/kg/day (n=49) from FOR-DMD to:

- vamorolone 2.0 mg/kg/day (n=28) or vamorolone 6.0 mg/kg/day (n=28) in the VISION-DMD study (up to 48 weeks), or
- vamorolone dosing between 2.0–6.0 mg/kg/day (n=46) in the VBP15-LTE study (up to 2.5 years)

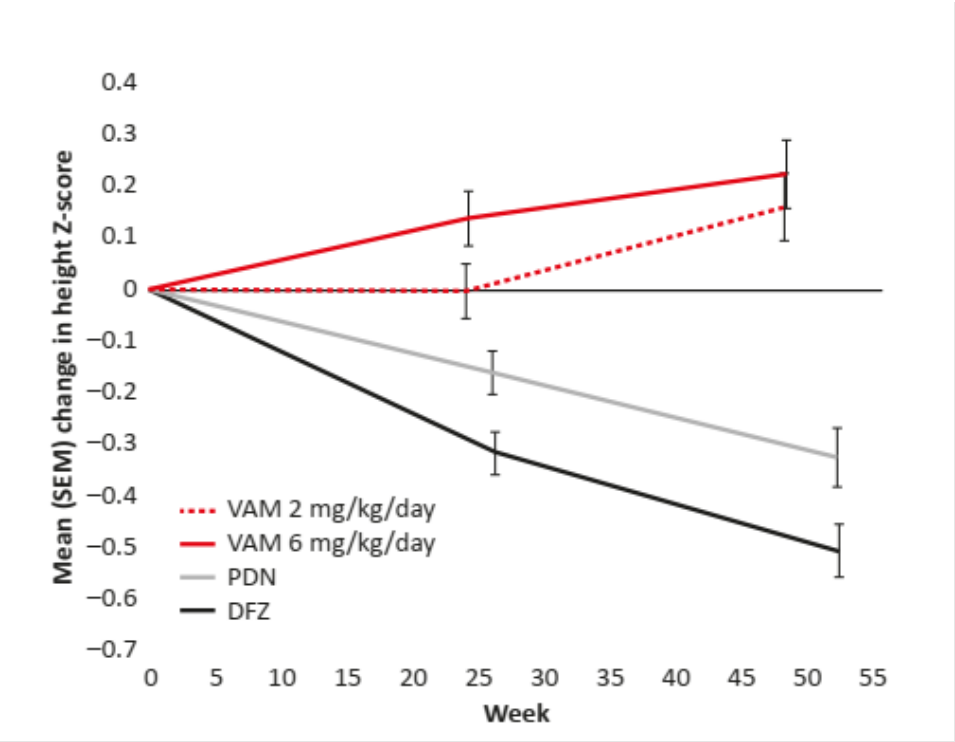
3.4. Critique of the indirect comparison and/or multiple treatment comparison

Despite the comparability of outcome measures between the trials in the indirect treatment comparison, the CS did not contain the results of clinical outcome measures across the treatment arms. The EAG was also unable to identify a publication of such an analysis. The

EAG considered that such a comparison would have augmented the evidence base for vamorolone by providing more evidence of its effectiveness in comparison to the alternative glucocorticoid treatments.

In the CS, the company reported difference in height Z-score after 1 year. The results showed that participants in the vamorolone arms had increased height Z-scores and participants in the prednisone and deflazacort arms had decreased height Z-scores from baseline. All changes were within one standard deviation of population norms.

Figure 6: Mean (SEM) change from baseline in height z-scores



Abbreviations: DFZ, deflazacort; PDN, prednisone; SEM, standard error of the mean; VAM, vamorolone

3.5. Conclusions of the clinical effectiveness section

The results of the company's clinical trials showed that participants receiving both vamorolone and prednisone showed meaningful improvements in muscle function compared to placebo after 24 weeks of treatment. However, vamorolone did not out-perform prednisone, and there were trends for vamorolone to have meaningfully poorer outcomes than prednisone after 24 weeks (Key Issue 1). Following this timepoint, participants receiving vamorolone did not show further

improvements, and treatment effects appeared to remain stable, potentially up to 30 months later. As there was no comparison arm in the trials beyond 24 weeks, it was not possible to determine whether clinical outcomes following treatment with prednisone would also stabilise or change.

On the balance of probabilities, the EAG considered it likely that vamorolone would not be as effective as prednisone in slowing down disease progression in muscle function. This conclusion was reached despite the lack of statistical significance in differences between vamorolone and prednisone at 24 weeks, which the EAG considered may be due to the small sample sizes in the trial and the anticipated variability in treatment outcomes for participants in all treatment arms. Further comparative evidence between vamorolone and prednisone (or deflazacort) at later timepoints would be useful for determining to what extent muscle function outcomes would be different with vamorolone. The EAG noted that the company could have reported the results of an indirect comparison between vamorolone trials and prednisone and deflazacort data from FOR-DMD. These data may have been informative for the appraisal, despite the limitations of naïve comparisons in general.

The EAG also noted that outcomes specified in the NICE scope that were not captured in the evidence base for vamorolone included short-term PROMs and medium- to long-term clinical outcomes that would demonstrate the implications of altered treatment effects on disease progression, such as the number of falls experienced by participants, and time to event outcomes for when people with DMD develop scoliosis or require use of a wheelchair. On the basis of the current evidence, it was therefore unclear to what extent any reduction in treatment effect with vamorolone would impact on the lives of people with DMD, including any long-term consequences.

As suggested by the company, the main potential benefit of vamorolone may be the reduced incidence of specific adverse effects that impact on the lives of people with DMD receiving existing treatment options, such as weight gain, stunted growth, behavioural issues and bone health. While data for these outcomes were based on short follow-up and were uncertain due to low event rates, the data were promising and suggested that the risks of these outcomes may be lower with vamorolone.

On the basis of the above conclusions, the EAG considered that vamorolone may be a preferred treatment option for some parents on the basis of its safety profile, despite the risk that it may not be as effective at maintaining muscle function as existing treatments. As is

current practice, parents may choose between vamorolone and existing treatments in order depending on their preferences and according to treatment response. This may mean that, contrary to the evidence available in the CS, vamorolone may be administered at a subsequent treatment line and not in a population who are naïve to glucocorticoids. The EAG considered it plausible that treatment effects for vamorolone may vary according to the line of treatment, though there was an absence of evidence to determine this (Key Issue 2). This was therefore a remaining uncertainty in the clinical effectiveness evidence for this appraisal.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted a SLR of previous economic evaluations, the searches for which were considered adequately structured and executed using a good range of sources. However, as noted in section 3.1, the EAG had some concerns over the quality of the search and its reporting. For example, only thesaurus terms were used to describe the interventions, and therefore the search may have missed articles not yet indexed, or poorly indexed. Zero search results are reported for Econlit, but when searched by PenTAG via EBSCOhost there were two relevant articles (although these were picked up via other databases in the company search). In addition, no details were provided of how supplemental searches were executed, and some numbers don't tally between the text and the Figure 1 PRISMA diagram.

The EAG was also unclear as to the extent to which the findings from the SLR informed the company's approach to patient utility assumptions and other model parameters. For example, from the economic evaluation SLRs, it seems that only one of the HRQoL studies retrieved from the search, Landfeldt 2017[22], was used in the building of the model. Rather, the company made extensive use of Noble-Longster et al 2022,[23] and Evans 2020[24], unpublished burden of illness (BOI) studies from the project HERCULES, which were not retrieved from the search. Many of the health state costs and resource data were also taken from these BOI studies, or other studies not retrieved from the search. There was therefore a lack of clarity in how the company selected the studies used to inform parameters in the model. However, given the model was based on the HERCULES natural history model, there is a logic to the use of the those data. Nevertheless, a full critique of other studies would have strengthened the company's choice of inputs. The EAG was therefore uncertain about the reliability of some of these resource and utility estimates used.

Table 26. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The company conducted a SLR of previous economic evaluations, the searches for which were executed using a suitable range of sources, although as noted in section 3.1, the EAG had

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		some concerns over the quality of the search and its reporting.
Inclusion criteria	Appendix G, Table 8	The inclusion PICO criteria were suitable for the decision problem. The company included cost-effectiveness, cost-utility analysis, cost-benefit and cost-minimisation analyses, and EEACTs (Economic Evaluation alongside Clinical Trials). Burden of disease, resource use and budget impact studies were excluded.
Screening	Appendix, D1.1	The EAG considered the methods for screening to be adequate. Only cost-effectiveness studies from a UK perspective were included.
Data extraction	Appendix, D1.1	The EAG was satisfied with the data extraction process.
QA of included studies	Appendix G, Table 12	Quality assessment was provided by using the Drummond and Jefferson criteria

Abbreviations: CS, Company Submission; EAG, External Assessment Group; EEACTs, Economic Evaluation alongside Clinical Trials; HRQoL, health-related quality of life; PICO, Population Intervention Comparator Outcome; QA, quality assessment; SLR, systematic literature review; UK, United Kingdom

Table 27. Summary of EAG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The company conducted a SLR of HRQoL articles relevant to the decision problem, the searches for which were executed using a suitable range of sources, although as noted in section 3.1, the EAG had some concerns over the quality of the search and its reporting.
Inclusion criteria	Appendix G, Table 9	The inclusion PICO criteria were suitable for the decision problem. The company included RCTs, non-RCTs, observational studies, HRQoL elicitation and validation studies, economic evaluations, cost-utility analyses, and EEACT (Economic Evaluation alongside Clinical Trials). Individual cost study reports were excluded.
Screening	Appendix, D1.1	The EAG considered the methods for screening to be adequate.
Data extraction	Appendix, D1.1	The EAG was satisfied with the data extraction process.
QA of included studies	N/A	No quality assessment was performed.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

Table 28. Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The company conducted a SLR of healthcare resource use and costs articles relevant to the decision problem, the searches for which were executed using a suitable range of sources, although as noted in section 3.1, the EAG had some concerns over the quality of the search and its reporting.
Inclusion criteria	Appendix G, Table 10	The inclusion PICO criteria were suitable for the decision problem. The company included the economic evaluation study types described above, plus cost, burden of disease and resource use studies. Individual case studies were excluded.
Screening	Appendix, D1.1	The EAG considered the methods for screening to be adequate.
Data extraction	Appendix, D1.1	The EAG was satisfied with the data extraction process.
QA of included studies	N/A	No quality assessment was performed.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 29: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate, which captured the health benefit to patients. The company included carer disutility within their base case.
Perspective on costs	NHS and PSS	The company included a number of non-reference case costs in its estimate of health state costs in its base case (eg

Attribute	Reference case	EAG comment on company's submission
		non-medical costs and transfer payments).
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis, presenting pairwise results versus a pooled comparator. The model submitted by the company was a Markov model. The EAG considered that the company's decision model was broadly appropriate for decision making but that a pooled comparator risks biasing estimates of incremental cost-effectiveness.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company used a 50 year time horizon in the base case analysis. The EAG considered that this was long enough to capture key differences in costs and QALYs between vamorolone and SoC over time.
Synthesis of evidence on health effects	Based on systematic review	Clinical data used in the economic model were derived from multiple sources inlcuding VISION DMD, FOR DMD and the long-term extension study (LTE). Additionally, the company used published literature and assumption when data were unavailable.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	EQ-5D scale was noted to lack sensitivity for DMD in the CS and hence condition specific preference based measure DMD-QoL has been used to derive patient utilities (as per BOI study[23]) and EQ-5D for carer utilities (based on Landfeldt et al 2017[22]).
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The company has used the QALY shortfall approach. A 1.7x severity modifier has been applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	Some resource use and costs were primarily based on NHS reference costs 2021/2022 and the PSSRU (2022), as

Attribute	Reference case	EAG comment on company's submission
	valued using the prices relevant to the NHS and PSS	appropriate. The EAG noted that health state costs were based on direct and indirect medical costs from a burden of illness study which included a number of out of scope items (eg out of pocket costs and transfer payments)[24]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and QALYs were discounted at 3.5% as appropriate.

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal; DMD-QoL, Duchenne Muscular Dystrophy Quality of Life Measure

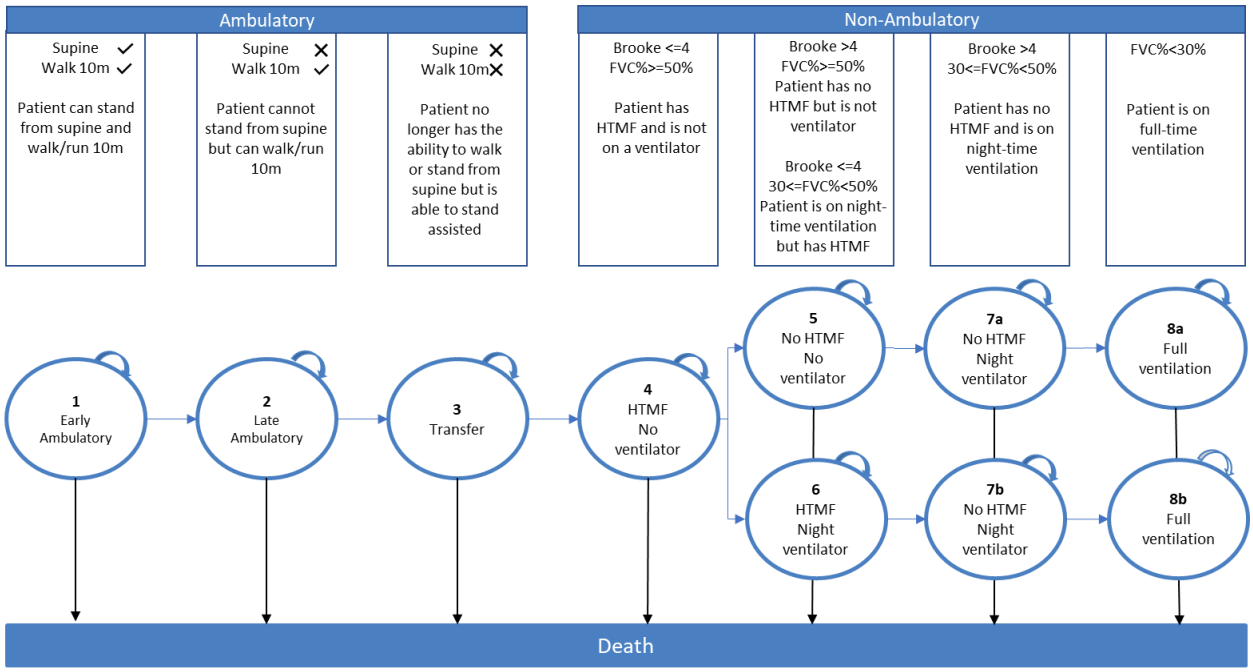
4.2.2. Model structure

The company's model was based on the HERCULES natural history model of disease progression of patients with DMD.[25] It comprised a Markov model consisting of eight health states, and death as the absorbing state. The health states were clearly defined and structured around a patient's ambulatory status, Brooke score[26] (with a cut-point at ability to self feed), FVC% and requirement for nocturnal or full time ventilation (Figure 7).

Patients progress through the model according to transition probabilities. Progression was only permitted towards more severe health states (i.e. disease reversal was not possible). This was consistent with clinical opinion to the EAG that characterised DMD as progressive in nature with no improvement in health status observed with time. Furthermore, the HERCULES model appeared to be appropriate to reflect the UK population with DMD.

The EAG considered the structure of the model to be appropriate to address the decision problem.

Figure 7: Model Schematic



Source: CS, Figure 21.

4.2.3. Population

The average starting age in the model was 4.1 years, based on a UK study by Vry et al.[27] It was not clear why the company opted to use Vry et al. to derive baseline age, as opposed to the pivotal trial (VISION DMD). It may have been due to the multicentred nature of VISION DMD and therefore relatively limited generalisability to UK patients, although 6/33 centres in the study were UK based. It was also consistent with the licensed starting age of 4 years. The company provided a sensitivity analysis which increased the starting age to 5.1 years, in line with the average age within VISION-DMD (5.41 years). Results were somewhat sensitive to this analysis.

Clinical opinion to the EAG confirmed that children with DMD are likely to start steroids at approximately 4 years of age, with most starting between the ages of 4 and 6 years. Overall, the EAG considered the company's base case age to be appropriate. However, for completeness a scenario analysis was conducted with a starting age of 5 years.

4.2.4. Interventions and comparators

The primary comparator included in the economic analysis was standard of care (SoC), which was assumed to consist of prednisone or deflazacort, expressed as a blended comparator assuming 85% of patients take prednisone and 15% take deflazacort (this affects costing estimates described in Section 4.2.8 below and some adverse events). Clinical opinion to the EAG was that both prednisone and deflazacort were considered standard of care in the UK, however the proportion of new patients receiving each treatment was approximately 50/50. It was also noted that prednisone was used more by older children. Deflazacort was not offered in soluble form, which may influence uptake.

The EAG has concerns with pooling of comparators as they introduce scope for gaming and evading relevant comparisons of interventions along the efficient frontier. The EAG's preferred approach is to treat discrete treatment strategies as such and compare all in a fully incremental analysis, as per the NICE reference case.

The model allowed for down titration of dosing based on tolerability (Table 30). Clinical expert opinion to the EAG was that dosing would be reduced only if there were intolerable side effects. There would be a period where dose is increased in line with weight, provided that patients have good ambulation. However, once patients become non-ambulatory the dose is not increased and is more likely down-titrated. Clinical opinion to EAG also indicated that while patients might experience reduced efficacy with down-titration, it would still be better than having no treatment. Parents may be reluctant to increase dose, particularly if the treatment is considered to increase behavioural problems. The impact of dosing on cost and outcomes is considered in sections 4.2.6 and 4.2.8.

Table 30: Dosing regimens in the economic model

Drug	Starting dosing regimen	Dose reduction regimen	Source
Intervention			
Vamorolone	Aged 4 years and older: 6.0 mg/kg/day administered orally	May be down-titrated to either the below based on individual tolerability: • 4.0 mg/kg/day administered orally • 2.0 mg/kg/day administered orally	SmPC[11]; VISION-DMD[4]
SoC			

Drug	Starting dosing regimen	Dose reduction regimen	Source
Prednisone	0.75 mg/kg/day administered orally	0.53 mg/kg/day administered orally	25-33% dose reduction based on Birnkrant et al.[28]
Deflazacort	0.9 mg/kg/day administered orally	0.64 mg/kg/day administered orally	

Abbreviations: SmPC, summary of product characteristics; SoC, standard of care

4.2.5. Perspective, time horizon and discounting

Costs were estimated from an NHS and PSS perspective (albeit with some out of scope costs, see section 4.2.8 below). Additional scenarios were conducted including a broader (societal) cost scope. Outcomes were considered from the perspective of the patient and one carer. Costs and benefits were discounted at 3.5% as per the NICE reference case.

The time horizon used in the company's base case was 50 years. The company noted that 50 years was likely to be appropriate as *'DMD is a life-long condition that reduces life expectancy significantly, with a median life expectancy of 29.9 years (range 21.0-36.2) with ventilatory support'* (Landfeldt et al. 2020[29], cited in company submission, Table 42, P108). Based on clinical input to the EAG, the median life expectancy for people with DMD born before 1990 was approximately 28.1 years. However, post-1990, median life expectancy was likely to be higher. Clinical opinion to the EAG further confirmed that people with DMD were not likely to live beyond the age of 50 years. Overall, the EAG considered that 50 years was long enough to capture key differences in costs and benefits between vamorolone and SoC.

The cycle length used in the model was one month (with half cycle correction). Based on clinical input to the EAG, patients in the UK were likely to be reviewed or assessed every six months by a clinician, thus a six month cycle length may also be appropriate. However, the shorter cycle length allowed for greater resolution and granularity in the results. The EAG considers the one month cycle length to be appropriate to the decision problem.

4.2.6. Treatment effectiveness and extrapolation

The company considered the follow-up of the pivotal RCT (VISION-DMD[10,11]) too short to provide reliable estimates of transition probabilities for the model. It therefore did not use these data, preferring to use transition probabilities reflecting the natural history of disease already employed in the HERCULES model.[25] This was supplemented with two additional studies, FOR-DMD[4] and LTE[14], for extrapolation of the effectiveness of SoC and vamorolone, respectively.

Transition probabilities were based on steroid dosage (whether for SoC or vamorolone): either on treatment (full dose), off treatment, or down-titrated dose.

On-treatment transition probabilities, SoC and vamorolone: Natural History Model

The company used the natural history transition probabilities to represent the disease progression for patients taking the full dose of vamorolone and prednisone (6.0mg/kg/day and 0.75mg/kg/day, respectively). This is justified on the basis of *"vamorolone… show[ing] comparable efficacy to prednisone… in VISION-DMD"* (Company submission, Section B3.3.2, P109). However, the EAG's review of the results of VISION-DMD concluded there was some evidence for the superiority of prednisone over vamorolone (section 3.2.3). Whilst the EAG broadly agrees that the short follow-up time of VISION-DMD limits the scope for generation of transition probabilities, the EAG disagrees that the assumption of equal efficacy represents a conservative approach and explores a number of alternative scenarios in its own analyses (Sections 6.2 and 6.3).

Natural history transition probabilities in the HERCULES model are based on pooled individual patient data from 11 data sources including natural history studies, placebo arms of clinical trials, and disease registries. Eighty per cent of the patient cohort were taking steroids, but the type and dosing regimen were not stated. The company acknowledges this as a source of uncertainty. On balance, the EAG considers the natural history model a suitable source for transition probabilities.

Off-treatment transition probabilities, SoC and vamorolone

McDonald et al. (2018)[2] reported Kaplan-Meier estimates of time to ambulatory milestones for patients on GC for over one year and for those who were either untreated or received GC for less than a month. The company assumed that the two arms represented on and off treatment for SoC and vamorolone. Hazard ratios were calculated from fitting a Cox proportional hazards model to each pair of curves representing time to certain milestones. Transition probabilities were modified by the estimated hazard ratios.

Overall, the EAG considered this approach somewhat crude and at high risk of bias but was reasonable and likely the best option given the data available.

Titrated dose transition probabilities, SoC

Data from FOR-DMD (2022),[4] an RCT of differing steroid dosing regimens in DMD, were reviewed to estimate hazard ratios for ambulatory milestones. The company stated the resulting HRs lacked face validity as they implied worse outcomes than no steroids. Clinical advice to the company was to adopt a 60% relative effect (i.e. a 40% reduction in effect). The company opted for a larger 40% relative effect (i.e. a 60% reduction in effect) in its base case as a mid-point between clinical opinion and the FOR-DMD data, exploring 60% (and 20%) in a scenario analysis. The EAG considered this a reasonable solution. It was, however, noted that this was applied only to the SoC arm, and not suboptimal dosing of vamorolone. Clinical advice to the EAG was that this was unlikely. The EAG therefore explored alternative scenarios in its analyses, and adopted a symmetric approach in its base case (see section 6.2.2).

Mortality

The HERCULES model does not implement an age-related mortality, with mortality dependent only on health state. The company therefore modified the transition probabilities for patients aged 30 and over from states 8a and 8b to death (doubling the mortality risk from ~0.32% per week to ~0.65%), following a review of an individual patient data meta-analysis.[30] The cut-off of 30 years was selected as the median survival of patients with DMD. In addition, age-specific mortality was compared with general population mortality, with the chosen value being whichever was the higher of DMD or general population levels. The EAG considered the adjustment for general population mortality to be plausible, but as the post-30 years of age increase represented a modification to what is designed as a natural history model, the EAG explored the impact of excluding the mortality boost at 30 years in a scenario.

Adverse events

Adverse events were divided into adverse events of special interest (AESIs) and acute events. In addition, the model also included stunted growth, incidence of fracture (spinal and other), and scoliosis.

AESIs included weight gain, behavioural issues, and Cushingoid features *inter alia*, whilst acute events were diarrhoea, vomiting, pyrexia (fever), and cough (Table 31 and Table 32). Data for AESIs and acute events for vamorolone and prednisone patients were extracted from VISION-DMD.[10,11] The placebo arm of VISION-DMD was used to represent the incidence of events for patients who were off treatment. Incidence of stunted growth in the prednisone arm was based

on a six-year follow-up of a case-series of boys receiving daily steroids.[6] The company assumed zero stunted growth in the vamorolone arm. Incidence of AESIs for down-titrated doses of prednisone were adjusted for rate ratios from FOR-DMD.[4] Adverse events were assumed the same in the vamorolone arm, regardless of dose.

The EAG noted that the company only included moderate to severe events in its primary analysis, despite an AESI being defined as any which is 'severe and sudden in onset' (company submission p118), although the company conducted a scenario including all adverse events. The EAG noted that excluding the less severe events resulted in a substantially lower incidence included in the model compared with the trial data (see Table 31 and Table 32 below). Whilst inclusion of only moderate and severe adverse events is a common pragmatic approach in decision modelling, given (1) the side effect profile of vamorolone vs other steroids is pivotal to the company's value proposition and (2) all AESIs being considered severe by definition, the EAG conducted scenario analyses around this.

Table 31: Adverse event rates per monthly cycle used in model

Treatment	Vamorolone	SoC (optimal dose)	SoC (sub-therapeutic dose)	Placebo	Source
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	VISION-DMD; rate over 24 weeks Sub-therapeutic SoC AE rates calculated from ratio in FOR-DMD.
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	
Cough	[redacted]	[redacted]	[redacted]	[redacted]	
Weight gain	[redacted]	[redacted]	[redacted]	[redacted]	
Behavioural issues	[redacted]	[redacted]	[redacted]	[redacted]	
Cushingoid effects	[redacted]	[redacted]	[redacted]	[redacted]	
Immune suppressed/infection	[redacted]	[redacted]	[redacted]	[redacted]	
GI symptoms	[redacted]	[redacted]	[redacted]	[redacted]	
Diabetes	[redacted]	[redacted]	[redacted]	[redacted]	
Skin/Hair change	[redacted]	[redacted]	[redacted]	[redacted]	
Stunted growth	0.00%	1.75%	1.44%	0.00%	Wong et al.; rate over 6 years

Abbreviations: AESI, adverse event of special interest; GI, gastrointestinal.
Source: Company Submission Document B Table 51, p118.

Table 32: Adverse events of special interest as reported in VISION-DMD (incidence over 24 weeks)

	Vamorolone 6.0 mg/kg/day (n=28)	Prednisone (n=31)	Placebo (n=29)	Vamorolone 2.0 mg/kg/day (n=30)
At least 1 clinically relevant AE	[redacted]	[redacted]	[redacted]	[redacted]
Weight gain	[redacted]	[redacted]	[redacted]	[redacted]
Behaviour problems	[redacted]	[redacted]	[redacted]	[redacted]
Cushingoid features	[redacted]	[redacted]	[redacted]	[redacted]
Infections	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic conditions	[redacted]	[redacted]	[redacted]	[redacted]
Skin/hair changes	[redacted]	[redacted]	[redacted]	[redacted]
Cataracts and glaucoma	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal disorder	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event
Source: VISION-DMD CSR[6], reproduced from Company Submission, Table 36, p82 (column and row ordering changed to match Table 31)

Bone Health

Fractures were modelled as a function of health state, with higher rates of spinal vertebral fractures associated with SoC (prednisone and deflazacort) versus vamorolone, and lower rates of long bone fractures for SoC versus vamorolone or no treatment, albeit with some variation by health state (Tables 52 and 53 of company submission, pp119-20). Rates for SoC and off treatment were based on long-term follow-up data of cohorts of patients who did and did not take steroids (Perera et al. 2016[5]), and those for vamorolone were extracted from the LTE study and FOR-DMD. Overall, the EAG felt the approach possessed face validity and was reasonable given the data constraints.

The impact of scoliosis was included in the model via estimates of the proportion of individuals requiring spinal fusion surgery. Data from McDonald et al. (2018)[2] suggested that 29% of non-ambulatory patients have spinal fusion surgery over 10 years. However, the cohort comprised mostly (87%) participants who had received steroids. Clinical expertise suggested that surgery amongst those receiving steroids would be around 10%, whilst 90% of those off steroids would require it. The EAG considered this a reasonable assumption.

Discontinuation

In Section B.3.3.5 of the CS, the company stated that the discontinuation data used in the economic model for vamorolone and SoC were taken from VISION-DMD and the Cooperative International Neuromuscular Research Group (CINRG), respectively. The company reported discontinuations in prednisone, deflazacort, and prednisolone using the chart in Figure 8.

Figure 8: SoC discontinuation from Cooperative International Neuromuscular Research Group

Source: CINRG. Reproduced from CS, Figure 23, Document B

While the company stated that these data are taken from CINRG, no further details were provided in the CS as to the specific publication in which they were reported. The CINRG discontinuation data was reported for longer than 14 years as opposed to 24 or 48 weeks in VISION-DMD. The EAG did not consider discontinuation data after less than a year of treatment could reliably be extrapolated to a lifetime as discontinuation data gathered over 14 years of treatment. Also, the EAG noted that the proportion still on deflazacort plateaus at ~82% after six years while prednisone and prednisolone continued to decline to below 30% by 14 years. This lacked face validity and was further queried by clinical advisors to the EAG. The EAG were unable to critique these data as the company did not detail which specific publication(s) they were taken from.

In terms of parametric extrapolation, the original CS mentioned that due to small sample sizes the standard set of parametric functions produced implausible results. Therefore, exponential functions were fitted to the data in the original model submitted by the company. However, following clarification, the company included the standard parametric curves in the updated model and proposed that log-logistic be used in the base case. The EAG, however, noted that generalised gamma fits the KM data for prednisone and deflazacort more closely than log-logistic and therefore implemented it in the EAG base case.

Vamorolone was stopped in the base case after progression to health state 6 (requiring night-time ventilation), with alternatives explored in a scenario analysis. Patients who stop taking vamorolone or SoC experience the transition probabilities and risk of adverse events of the no treatment arm. Clinical advice to the EAG was that in the past it was common to stop steroid treatment on loss of ambulation, but patients may now continue after this point. However, treatment would not necessarily be ceased at health state 6. The EAG therefore explored an alternative stopping scenario (at loss of ambulation) based on the clinical advice received.

Down-titration

As well as discontinuation, the model allowed down-titration of dose (with associated transition probabilities described above). For SoC this was based on CINRG data, and for vamorolone, data from the named patient programme (NPP). The EAG noted that the impact of down titration was applied asymmetrically. That is, while patients on SoC who reduced their dose would experience reduced treatment effects (see the description of transition probabilities above), side effects, and lower drug acquisition costs, patients who reduced dose on vamorolone would maintain a full treatment effect (and side effects), but with lower drug acquisition costs. While clinical advice to the EAG confirmed that residual benefits are likely to be maintained post treatment cessation, the EAG did not consider the asymmetric approach to be plausible, and therefore explored alternative scenarios.

4.2.7. Health-related quality of life

EQ-5D data were collected within the VISION-DMD trial. However, the company cited evidence that EQ-5D is of limited sensitivity to changes in health status in people with DMD and therefore excluded these data from their analysis. The company's systematic review instead identified a number of studies reporting health state utilities, from which the company selected Landfeldt et al. (2017)[22] as the most appropriate. This used the HUI3 questionnaire to measure health status

of patients and was proxy completed by carers. Carers themselves completed the EQ-5D-3L to rate their own health status. An additional burden of illness (BOI) was identified (Noble-Longster et al. 2022[23]), conducted as part of the project HERCULES model, using the disease specific DMD-QoL.

The company's base case used patient utilities from the BOI study, and a blend of the Landfeldt and BOI studies for carer disutilities. to ensure consistency and face validity. Landfeldt et al. (2017) was used in scenario analyses.

Disutility due to adverse events was drawn from a number of sources, including previous technology appraisals. The EAG considered the magnitude of utility decrements to be broadly reasonable, but explored alternative value sets (section 6.2.10).

4.2.8. Resources and costs

4.2.8.1. Drug costs

Drug costs for vamorolone included a confidential patient access scheme (PAS) discount. List prices for deflazacort and prednisone were extracted from the BNF. The EAG noted that drug costs are linked to body weight, as the dosing is body weight dependent. However, there was no banding of dosing based on body weight mentioned in the CS. Also, the company assumed no change in body weight beyond 18 years of age. They instead applied a consistent body weight of 66.5 kg (the UK general population's 50th percentile weight). The EAG clarified the appropriateness of this assumption with a clinical expert, who mentioned that this assumption is not unreasonable given that for most boys with DMD weight gain happens before 18 years of age; they are less likely to gain weight beyond this. Although the possibility of weight gain beyond 18 years cannot be ruled out completely, the proportion of such patients is expected to be low. All treatments are oral and thus there were no administration costs, and zero wastage was assumed. Clinical advice to EAG confirmed that drug wastage is likely to be minimal. The EAG was confident that drug costs had been modelled appropriately.

4.2.8.2. Health state costs

Costs by health state were extracted from the BOI study, a part of project HERCULES. The study included direct medical care costs (excluding paid carer time, which may have been funded privately or provided by personal social services), as well as direct non-medical care costs. The EAG noted that direct medical costs included tests and procedures, medical devices, consultations, and hospitalisations. However, non-medical costs included home alterations, over

the counter medications, transport, transfer payments, alternative therapies, and ‘other’ costs. Home alterations may be funded by personal social services. However, over the counter medications, transport and alternative therapies represent patient out of pocket costs, and transfer payments are not funded by the NHS. Therefore, a substantial proportion of the health state costs are out of scope and are therefore inconsistent with the reference case. The EAG explored the impact of excluding the out of scope costs in scenario analysis.

4.2.8.3. Adverse event costs

The company assigned resource use associated with adverse events based on assumed contact with the health service. The EAG considered most of the unit costs assigned to be appropriate. The exceptions were the cost of growth hormone therapy for stunted growth (£6,451 per patient per year) and inclusion of indirect costs for spinal surgery for scoliosis. Clinical advice to the EAG suggested that growth hormones are rarely used in DMD in the UK, and indirect costs are out of scope of the reference case. Therefore the EAG explored a scenario excluding this cost.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

The company submission stated that a patient access scheme (PAS) discount for vamorolone is pending approval. This discount of [redacted] was incorporated into their model. Based on the deterministic results provided by the company, vamorolone, with the PAS discount, gave an ICER of [redacted] compared to SoC – based on an incremental QALY gain of [redacted] and an incremental cost of [redacted] (Table 33). Probabilistic results yielded higher incremental costs and lower incremental QALYs compared with the deterministic, resulting in an ICER of [redacted] (Table 34). The model from which these results are taken included a log-logistic parametric extrapolation of the proportion on treatment, which the company requested be considered the revised base case rather than that reported in the updated submission (see clarification response v2.0, Table 18 vs updated company submission, Table 78 P152). The company did not report probabilistic analyses in the clarification response but were available in the decision model.

Table 33: Company base case results (PAS price) – deterministic

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALY, Quality-adjusted life year; SoC, standard of care

Table 34: Company base case results (PAS price) – probabilistic

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£)
SoC	[redacted]	nr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	nr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; nr, Not Reported; QALY, Quality-adjusted life year; SoC, standard of care

5.2. Company's sensitivity analyses

The results of the company's sensitivity analyses, including one-way sensitivity analyses (OWSA), scenario analyses and probabilistic sensitivity analyses (PSA), are outlined in the sections below.

5.2.1. One-way sensitivity analysis (OWSA)

The company provided a OWSA, which varied key model parameters from upper and lower CIs derived from literature or estimated from the pre-specified probabilistic distributions assigned to each parameter. The results are presented in Table 35.

The EAG noted three key matters pertaining to this analysis:

- The results were relatively insensitive to variation of the modelled parameters. The highest ICER was reported to be [redacted].
- No justification was provided for selecting the relatively short list of model input parameters.
- Although OWSA is useful in identifying the parameters that are likely to impact base case results, the EAG believed that the analysis was not useful to inform decision making. This was because parameters were varied individually and without context.

Table 35: Company OWSA results

Parameter name	Lower incremental costs	Upper incremental costs
Direct costs by health state (CPRD) - Comparator 1: 8 - Full time ventilation	[redacted]	[redacted]
Direct costs by health state (CPRD) - New treatment: 8 - Full time ventilation	[redacted]	[redacted]
Direct costs by health state (CPRD) - New treatment: 1 - Early ambulatory	[redacted]	[redacted]
Behavioural issues: Disutilities	[redacted]	[redacted]
Stunted Growth Costs	[redacted]	[redacted]
Behavioural issues: Caregiver Disutilities	[redacted]	[redacted]
Behavioural issues (caregiver): Duration of event (days)	[redacted]	[redacted]
Vamorolone - Average weight: Age 5	[redacted]	[redacted]
SoC Behavioural issues incidence per cycle: 8b - Full time ventilation	[redacted]	[redacted]

Abbreviations: BOI, burden of illness; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; OWSA, one-way sensitivity analysis; PAS, patient access scheme; QALY, Quality-adjusted life year; SoC, standard of care

5.2.2. Scenario analyses

The company provided scenario analysis results based on the original model using both list and PAS prices for vamorolone, as presented in Table 36 and Table 37. The EAG was initially unable to replicate some of the scenario results. Nonetheless, following clarification, the company provided the model settings used for those scenarios in their updated model.

Table 36. Company's scenario analyses results for vamorolone vs SoC – PAS price

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

Table 37. Company's scenario analyses results for vamorolone vs SoC – list price

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

Abbreviations: ICER, Incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALY, Quality-adjusted life year; SoC, standard of care

5.2.3. Probabilistic sensitivity analysis

The company conducted a probabilistic analysis with 1,000 simulations but did not provide any analyses to demonstrate whether this was sufficient to minimise Monte Carlo error. Probabilistic results are reported above in Abbreviations: ICER, Incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALY, Quality-adjusted life year; SoC, standard of care

Table 34.

5.3. Model validation and face validity check

The company's model was based on the project HERCULES natural history model, with amendments reviewed by clinical experts for plausibility. The company also compared its estimates of QALYs accrued in the SoC arm with previously published studies.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations with the company's base case, and therefore explored the impact of using alternative assumptions and parameter values. The section is organised as follows:

- 6.1 details the impact of errors identified in the EAG's validation of the company's model.
- 6.2 presents a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and uncertainties identified by the EAG. These analyses were conducted within the company's (post-clarification) base case analysis.
- 6.3 presents the EAG's preferred base case, in both an incremental and cumulative manner.

6.1. EAG corrections and adjustments to the company's base case model

Besides several minor errors in terms of reporting, labelling and discrepancies between the CS (Document B) and the model, the EAG noted the following issues:

- The company's economic model applied a severity modifier to both patient and carer QALYs. The severity modifier is based on the QALY shortfall. However, as described in NICE guidance, "…QALY shortfall is defined as the amount of health lost by a person with a condition; other people, such as carers, should not be included".[31] The EAG therefore corrected this by applying the modifier only to patient QALYs.
- EAG noted a #VALUE! error in the probabilistic model parameters for generalised gamma (Cost Calcs sheet). This prevented the running of the PSA using a generalised gamma parametric extrapolation. The EAG did not have access to the data used to derive these parameters. However, it was identified that the variance (Q) in the covariance matrix was negative. This was subsequently fixed, which enabled the PSA to run. Nevertheless, the EAG is uncertain whether the fix applied fully resolved the issue, unless clarified further by the company.
- A formula was also found to be missing (in the 'HRQoL data' sheet of the model) for choosing patient utility values based on either the BOI study or Landfeldt et al. 2017. The sheet instead contained hard coded values based on BOI study rather than a formula

linking to HRQoL calculations. The EAG subsequently fixed this issue. No changes in the results were caused.

The EAG corrected company base case results – following the above changes – have been provided in Table 38 (disaggregated into the three discrete comparators with fully incremental analysis).

Table 38: EAG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company probabilistic base case					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted several scenario analyses to explore uncertainty surrounding certain model parameters and assumptions. The scenario analyses are listed below, with the associated results presented in Section **Error! Reference source not found.**.

6.2.1. Using an alternative starting age of the cohort

The EAG conducted an analysis in which the starting age of cohort was set to 5 years. This was based on clinical opinion to the EAG, which stated that starting the treatment was often delayed until 5 years of age, owing to delays in diagnosis. This scenario increased the ICER by 13%, as the total QALYs reduced slightly with the increased starting age. However, the results of this scenario should be interpreted with caution as the impact on treatment effectiveness or discontinuation could not be estimated (section **Error! Reference source not found.**).

6.2.2. Applying symmetric effect of down-titrated dose of SoC and vamorolone

In its base case the company assumed patients receiving standard of care would experience reduced treatment effectiveness, adverse events exposure and drug cost if the dose was down-titrated. Patients receiving vamorolone would experience maintained treatment effect, adverse events exposure but reduced cost. Clinical advice to the EAG was that this was unlikely. Therefore, the EAG implemented a symmetric approach to down-titration of dose. Ideally, it would have preferred to reduce the treatment effect and AE profile of vamorolone to mirror that in the SoC arm. However, the structure of the model prohibited this, therefore the EAG removed the impact of the reduction in dose on treatment effect and AE exposure in the SoC arm. In this scenario, as the total QALYs increased in both prednisone and deflazacort arms, owing to an increase in proportion on treatment, the incremental QALYs reduced thereby increasing the ICER (vamorolone vs prednisone) by 46%.

6.2.3. Applying an alternative SoC definition (prednisone and deflazacort proportions)

Clinical opinion to the EAG suggested that the split between prednisone and deflazacort in the UK is now nearer 50:50 (assumed as part of SoC; see Section 4.2.4 for more details), rather than the 85:15 assumed by the company. Therefore, the EAG conducted a scenario analysis with a 50:50 split to assess its impact on the cost effectiveness estimates. While drug costs were similar for prednisone and deflazacort, the two drugs varied in their safety profiles and the proportions of patients discontinuing in the long term. Because of this, the total QALYs were found to increase in SoC, leading to a reduction in the incremental QALYs gained for vamorolone and a 17% increase in the ICER. Note this scenario is incompatible with the EAG's preference for fully incremental analysis of discrete treatment strategies. The results are therefore presented in Table 40 (section **Error! Reference source not found.**).

6.2.4. Stopping treatment (for both vamorolone and SoC) at loss of ambulation

Clinical advice to the EAG indicated some uncertainty – in terms of real-world clinical practice – around the appropriate disease stage for stopping treatment, and indeed whether stopping was required at all. This was the case for both vamorolone and SoC. Although clinical advice indicated that stopping treatment at health state 6, as assumed in the company's base case, was not unreasonable, it was also confirmed that some clinicians may reasonably decide – in

consultation with patients and their families – to stop treatment at loss of ambulation. This scenario explored the impact of this uncertainty on the cost-effectiveness. It led to a reduction of 24% in the ICER, owing to reduced treatment costs because of early discontinuation (section **Error! Reference source not found.**).

6.2.5. Alternative rates of stunted growth and behavioural issues for vamorolone in the long term

The company assumed that people on vamorolone had zero stunted growth and – compared to SoC – a reduced incidence of behavioural issues. However, it was not clear in the company submission how the mechanism of action of vamorolone differs sufficiently from other glucocorticoids for such an assumption to be made. Therefore, EAG explored two scenarios 1) assuming that there would be small proportion of patients (5%) who would be experiencing stunted growth and behavioural issues in the long term with vamorolone 2) assuming that stunted growth and behavioural issues in the long term with vamorolone would be the same as SoC. While the smaller proportion assumption of 5% (1) was considered in the EAG base case, assuming to be the same as SoC (2) was considered as a scenario.

While assuming 5% events in the long term increased the ICER only by 4%, assuming it to be the same as SoC had tangible impact on the ICER (an increase of 24% was noted). This is due to the reduction in QALYs with vamorolone because of: disutility associated with stunted growth and behavioural issues, and the costs of growth hormone injections.

6.2.6. Excluding any additional mortality risk for patients over 30 years of age

In the company's base case, transition probabilities were modified for patients aged 30 and over from health states 8a and 8b to death, thereby applying a higher mortality risk to those patients. As this a deviation from the natural history model, the EAG explored the impact of excluding this additional mortality risk for patients aged 30 and over. An increase in total costs, life years and QALYs were noted across the treatment arms, with a net effect of a slight reduction of 5% in the ICER compared to the company's corrected base case (section **Error! Reference source not found.**).

6.2.7. Estimating vamorolone long-term discontinuation based on deflazacort and prednisone CINRG data

The company's base case used relatively short-term (<1 year) discontinuation data from trial for vamorolone, compared to the long-term (~14 years) discontinuation data available for SoC treatments based on CINRG. In contrast, the EAG base case assumed that vamorolone long-term discontinuation rates were the same as those seen for deflazacort (taken from the CINRG data) and extrapolated using a generalised gamma distribution beyond the observation period, as it was the distribution found to best fit the CINRG KM data. Deflazacort data was chosen for vamorolone discontinuation in the base case as their KM curves were found to be similar. There is also the expectation of better adherence to vamorolone versus prednisone owing to fewer side effects. As with the deflazacort CINRG data, the proportion on treatment in this scenario in the long term increased. The ICER increased substantially by 144%, mainly due to increase in vamorolone drug costs.

To explore further the uncertainty associated with this assumption, the EAG also implemented a scenario where vamorolone discontinuation data were assumed to be the same as prednisone (again based on the CINRG data). This scenario resulted in a proportion on treatment in the long term that was lower than that of deflazacort, but still higher than the vamorolone discontinuation rates (extrapolated using trial data) used in company base case. This resulted in increased treatment costs with vamorolone and an increased ICER of 73%.

6.2.8. Increased adverse events profile

The company included only moderate to severe adverse events in its estimate of the incidence of adverse events, despite all adverse events being defined as "severe and of sudden onset". The EAG therefore included the company's scenario including all adverse events in its analyses, in order to compare against the EAG corrected company base case.

6.2.9. Excluding carer QALYs

The company's modelled base case considered both patient and carer QALYs. In this scenario, the EAG explored the impact of not including carer QALYs. This was considered a useful scenario because of the uncertainty regarding the number of carers typically needed for a person with DMD, and the general lack of robust utility estimates. A substantial increase of 132% was observed in the ICER, as not considering carer QALYs resulted in a considerable reduction in incremental QALYs (section **Error! Reference source not found.**).

6.2.10. Using alternative health state utility values from the literature

This scenario explored the impact of alternative patient utility estimates (based on EQ-5D-3L) from Landfeldt (2023)[32] on the cost-effectiveness results. Landfeldt reported these values from an international cohort of patients,[33] where 58% of participants were from the United States or the United Kingdom (combined percentage reported in the paper). As the utilities for late ambulatory stages were relatively lower in Landfeldt, the total QALYs with the treatments reduced, resulting in a slight increase in QALY gain and a slight reduction in ICER (1%, section **Error! Reference source not found.**).

6.2.11. Excluding out-of-scope non-medical costs

The health state costs based on the BOI study in the company's base case included some out-of-scope non-medical costs. These included OTC medications, transport, alternative therapies, and transfer payments. The company's unit cost estimates for spinal surgery for scoliosis also included indirect costs. The EAG explored a scenario where these costs were excluded. Specifically, health state costs included all items in the CS (Table 67: Tests and medical procedures, medical devices, consultations and hospitalisations), plus only home alterations (from Table 68), based on the assumption that these would be paid for by social services. Indirect costs were excluded from the cost of treatment for scoliosis/spinal fusion surgery (last item of Table 72). Though a reduction in health-state related costs were noted in both treatment arms, the magnitude of reduction was higher with vamorolone. This is because more patients stayed in less severe, and therefore less costly, health states. This led to a slight reduction in incremental costs and a reduction of 1% in the ICER.

6.2.12. Excluding growth hormone costs for stunted growth

Clinical advice to the EAG suggested that growth hormone treatments are rarely used in DMD in the UK. Therefore, the EAG investigated the impact of excluding growth hormone therapy costs and included it in the preferred assumptions. As the adverse event costs reduced in the prednisone arm, an increase in incremental cost was noted, resulting in a 14% increase in the ICER (vamorolone versus prednisone). However, as AE costs substantially reduced for deflazacort, given that stunted growth is relatively more prominent in the deflazacort arm, the ICER for deflazacort versus prednisone reduced by 87% and it was no longer extendedly dominated by prednisone.

6.2.13. Using a 1x and 1.2x severity modifier

Based on the absolute QALY shortfall of [redacted] observed for prednisone and [redacted] observed for deflazacort in the EAG probabilistic base case (as given in Table 42, Reference case), a QALY modifier of 1.2x has been used in the EAG's base case. However, in this scenario, the EAG explores the impact of having no QALY modifier (i.e., a multiplicator of 1x) on cost-effectiveness. An increase of 47% in ICER was observed compared to company base case, owing to the reduction in incremental QALY gain with a lower QALY modifier.

6.2.14. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results of the EAG's exploratory and sensitivity analyses described above are provided in Table 39 and Table 40. Each change has been made individually and results are presented as fully incremental analyses, disaggregating the blended comparator of SoC into prednisone and deflazacort. Only deterministic analyses are presented, with both deterministic and probabilistic results presented for the EAG's preferred base case.

Table 39. EAG's exploratory analyses (deterministic)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)	% change from EAG corrected company base case
EAG corrected company base case						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Cohort starting age = 5 years						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13%
Symmetric impact of down-titration of treatment dose						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46%
Treatment stopping at loss of ambulation (based on clinical advice to EAG)						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-24%
Stunted growth and behavioural issues with vamorolone 5%						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4%
Stunted growth and behavioural issues with vamorolone same as SoC						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24%
No additional mortality risk for patients aged over 30 years						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-5%
Vamorolone discontinuation assumed to be the same as deflazacort (CINRG data)						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	144%
Vamorolone discontinuation assumed to be the same as prednisone (CINRG data)						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73%
Increased adverse events profile						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-97%
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19%
Exclude carer QALYs						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	132%
Alternative utility values (EQ-5D-3L) based on Erik Landfeldt, 2023[32]						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-1%
Exclude out-of-scope costs						

Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-1%
Exclude growth hormone costs						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-87%
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14%
QALY severity modifier = 1x						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47%
QALY severity modifier = 1.2x						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29%

Abbreviations: EAG, External Assessment Group; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 40. Alternative SoC definition (50% prednisone and 50% deflazacort)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	% change from EAG corrected company base case
EAG corrected company base case						
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC (85:15)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 50:50 (50% prednisone and 50% deflazacort)						
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18%
SoC (50:50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

6.3. EAG's preferred assumptions

The EAG incorporated the following assumptions for its preferred base case:

- Prednisone and deflazacort were considered as individual comparators with fully incremental analysis and the adverse event rates adjusted accordingly. The company base case used a blended SoC comparator.

- SoC patients on reduced dosages were assumed to remain at full SoC efficacy rather than reduced efficacy. This assumption was made to be consistent with the same assumption that had been made in the company base case for vamorolone (implemented by setting the proportion on 'full efficacy' following down titration to be the same as proportion on treatment in the 'Engine_2' sheet of the model). (Note it would have been preferable to apply a reduced effect to reduced dose for vamorolone to match SoC rather than the other way around but the model structure did not enable this).

- It was assumed that long-term rates of stunted growth and behavioural issues, experienced as moderate/severe AESI, would both be 5% for people on vamorolone. This was based on clinical advice to the EAG that patients might experience these side effects in later years. The company's base case assumed a rate of 0% for both.

- Vamorolone treatment discontinuation rates were assumed to be the same as deflazacort, based on long-term (approx. 14 years) CINRG data. Deflazacort data was chosen as its KM curve closely resembled that of vamorolone (based on EAP data presented in the clarification response) and because better adherence (versus prednisone) might be expected given the improved side effect profile claim for vamorolone. The company base case, however, used short-term trial data (48 weeks), subject to uncertainty beyond a year. Also, a generalised gamma parametric extrapolation of the proportion of patients discontinuing treatments in the long term was used as it fitted the KM curves of prednisone and deflazacort (based on CINRG data) more closely than the log-logistic used in the company's base case.

- Non-reference case health state and spinal fusion surgery cost items were excluded from the analysis.

- Growth hormone costs were excluded from the analysis on the basis of clinical opinion to the EAG.

- A QALY multiplier of 1.2x was used as the likely absolute QALY shortfall (based on the EAG base case) was observed to be between 12 to 18. The EAG also noted that there is uncertainty around the absolute QALY shortfall, as expected QALYs for the general population were based on EQ-5D-3L while QALYs for people living with DMD were derived using DMD-QoL (a disease specific QoL instrument).

The results of these changes, presented in Table 41, are shown both in terms of their isolated and collective impact.

Table 41. EAG's preferred base case assumptions (applied individually)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)
EAG corrected company base case					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symmetric impact of down-titration of treatment dose					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% stunted growth and behavioural issues with vamorolone in long-term					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation extrapolated using gen-gamma with vamorolone discontinuation assumed same as deflazacort CINRG data					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude out-of-scope costs					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude growth hormone costs					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.2x QALY multiplier applied					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (deterministic)					

Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (probabilistic)					
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

6.4. Conclusions of the cost-effectiveness section

Based on the EAG's preferred assumptions in the base case, in boys with DMD aged 4 and older, vamorolone resulted in a fully incremental ICER of [redacted]. This is calculated from an additional cost of [redacted] over deflazacort, for a QALY gain of [redacted] (over a 50-year time horizon), in the deterministic analysis at the PAS price. The probabilistic analysis resulted in a similar QALY gain ([redacted]) for an additional cost of [redacted] resulting in an ICER of [redacted]. Both figures are substantially higher than the willingness-to-pay threshold of £30k/QALY. Therefore, vamorolone is not likely to be a cost-effective treatment option for this population based on the current PAS and EAG's model assumptions.

The key drivers of cost-effectiveness were:

- treatment discontinuation of vamorolone in the longer-term,
- efficacy assumptions following down-titration or dose reduction of treatments,
- the long-term safety profile of vamorolone, especially related to stunted growth and behavioural issues,
- whether carer QALYs are considered, and
- the severity modifier (1.7 or 1.2) applied.

The EAG considered that the company's model structure, based on project HERCULES, adequately captured disease progression via the health states modelled. However, the EAG was concerned about the blended comparison of prednisone and deflazacort (versus vamorolone) as it prevented evaluation of interventions along the efficient frontier. To enable a fully incremental analysis, and to capture the distinct safety profiles of prednisone and deflazacort, the EAG preferred distinct comparison with the two separate SoC treatments.

Furthermore, the key assumptions driving the model – especially those related to treatment effectiveness and discontinuation – were associated with high uncertainty. This was reflected through a substantial increase in the ICER (versus the company's base case) when the EAG's preferred assumptions were implemented. While several EAG scenarios explored uncertainties around the company's modelled analyses, these should only be seen as a starting point towards addressing those uncertainties.

Finally, the QALY shortfall, calculated for current SoC treatments based on EAG's analyses, indicated that 1.2x should be applied as a disease severity modifier. This contrasted with the company's use of a 1.7x modifier.

7. QALY MODIFIER

NICE's severity modifier considers disease severity based on QALY shortfall. Inputting the EAG base case probablistic results into the Schneider et al. QALY Shortfall Calculator[34], the shortfall value qualifies for a disease severity multiplier of 1.2x. For the EAG base case deterministic analysis, the QALY shorfall is slightly higher, but still within the 1.2x multiplier range. Application of the EAG deterministic scenarios for mortality risk (for patients aged 30 and over) and a 50:50 prednisone/deflazacort split (for SoC) decreased the QALY shortfall slightly, though remainig within the range meeting the 1.2x criteria.

The original company model showed a QALY shortfall of slightly more than 18 ([redacted]). Hence the 1.7x multiplier was applied. The company's updated model, following clarification and EAG corrections (as per Section 6.1), revealed a slightly reduced QALY shortfall of [redacted].

On the other hand, the proportional QALY shortfall from the EAG's base case did not meet the threshold for applying a QALY weight of 1.2, as it was found to be less than 0.85.

Table 42 below provides a summary of the QALY shortfall analysis using the EAG base case (probabilistic) for reference case, as well as alternative cases or value sets. In all cases, the absolute QALY shortfall was found to be less than 18, and the proportional QALY shortfall was found to be less than 0.85.

Table 42. QALY shortfall analysis using EAG base case assumptions

Schneider shortfall calculator	Expected total QALYs for general population	Total QALYs (DMD-QoL) that people living with a condition would be expected to have with current treatment	QALY shortfall
Reference case: MVH value set + HSE 2014 ALDVMM model			
Prednisone	24.90	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Deflazacort	24.90	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Alternative A: 5L to 3L mapping (Hernandez Alava et al) + HSE 2017-18			
Prednisone	24.08	[redacted]	Absolute shortfall: [redacted]

Schneider shortfall calculator	Expected total QALYs for general population	Total QALYs (DMD-QoL) that people living with a condition would be expected to have with current treatment	QALY shortfall
			Proportional shortfall: [redacted]
Deflazacort	24.08	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Alternative B: 5L to 3L mapping (van Hout et al) + HSE 2017-18			
Prednisone	24.07	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Deflazacort	24.07	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Alternative C: MVH value set + health state profiles			
Prednisone	24.66	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Deflazacort	24.66	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Alternative D: MVH value set + HSE 2012-14			
Prednisone	24.94	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]
Deflazacort	24.94	[redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]

Abbreviations: EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level; HSE: Health Survey for England; MVH: Measuring and Valuing Health; QALYs, quality adjusted life-years; DMD-QoL, Duchenne Muscular Dystrophy Quality of Life Measure

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