Single Technology Appraisal

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Contents:

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NICE National Institute for Health and Care Excellence

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 24 April 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):c	Santhera

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Disclosure **Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]** **Please state:** • **the name of the company** • **the amount** • **the purpose of funding including whether it related to a product mentioned in the stakeholder list** • **whether it is ongoing or has ceased.**	[Insert disclosure here]
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Company commitment to providing access for patients** The Company is committed to the NICE process in bringing vamorolone to eligible patients living with Duchenne muscular dystrophy (DMD). The company welcomes the opportunity to comment on this Appraisal Consultation Document (ACD), provide additional information to NICE and other relevant stakeholders, and urge the Committee to reconsider the recommendation published in the ACD, to ensure that patients in England and Wales can access this medicine as quickly as possible.

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	As part of this response, the Company have attempted to align with the committee's preferred assumptions outlined in the appraisal consultation document, specifically: • Presented results in a fully incremental analysis. • Included a scenario which assumes a difference in muscle function outcomes between treatments based on VISION-DMD1 results. Scenarios assuming a reduction by 5% and 10% in efficacy between vamorolone and each of the comparator, applied to the HR, are presented. • Aligned with the EAG's preferred assumptions for vamorolone discontinuation. • Excluded growth-hormone and non-reference costs. • Used a QALY weight of 1.7 to patient QALYs only. The Company have addressed concerns raised by the Committee and External Assessment Group (EAG) in the appraisal consultation document by conducting the following additional analyses: • Further modelling of adverse events, including all VISION-DMD adverse event data (mild and moderate to severe AESIs); robust assessment of deflazacort adverse events based on FOR-DMD; analysis of long-term UK incidence data for rate of fracture from the NorthStar registry2 and long-term CINRG data for the rate of cataracts for patients on steroid treatment; and comparison of steroids vs. vamorolone for fracture and cataracts using CINRG data and the vamorolone long-term safety pool. Finally, a correction was implemented to the application of adverse events and spinal surgery. • The assumptions behind adverse events modelling have been validated by further three UK clinical experts, in particular considering the impact of behavioural issues. • Provided further data regarding dose-reductions, namely: long-term CINRG data showing the effect of dose reduction with prednisone and deflazacort on outcomes, and comparison of outcomes with vamorolone 4mg and 6mg arms. • A mortality cap has been applied to ensure that the per-cycle risk of death is never lower than age- and sex- matched general population mortality, or from the post-1990 cohort of Broomfield et al. 2021.3 • A longer time horizon of 95 years has been applied to capture the small proportion of patients still alive after a time horizon of 50 years. The model was reviewed by an external modelling expert, who validated the application of adverse events in the model as part of their review.

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	The Company have made further changes to the model base case to better align with UK practice, namely: • Incorporation of two carers in non-ambulatory health states to better reflect carer burden of DMD. • Correction to the application of hazard ratios (HR) from McDonald et al. 20184 following validation with a clinical expert in March 2024, who advised that the efficacy of full dose steroids compared to no treatments would remain the same in all health states, and any reduction in efficacy seen in the McDonald et al. 2018[4] paper is a result of patients' being down-titrated. • Updated health state costs to use the Landfeldt et al. 2017[5] publication which was used in the NICE appraisal for ataluren in DMD.[6] • Updated health state utilities to use Landfeldt et al. 2023[6] publication to ensure better alignment with NICE reference case. This data source was also accepted in the recent NICE appraisal for Ataluren in DMD.[6] • Implementation of bisphosphonate costs in line with UK usage. • Inclusion of mild adverse events resource use costs and amending moderate to severe adverse events resource use in line with clinical feedback on current practice. • Inclusion of loss of ambulation following fracture for a proportion of patients, to reflect clinical feedback received during the appraisal committee meeting. In addition, the Company has implemented a stopping rule at nighttime ventilation, following which no costs or benefits are applied to vamorolone patients. This is to reflect the lack of robust data to demonstrate adequate benefit risk. Currently, no patients receiving vamorolone as part of the expanded access program are receiving nighttime ventilation. **What is the current unmet need of DMD patients?** The Company welcomes the Committee's conclusion that there is a need for an effective treatment for DMD with less side effects than standard corticosteroids (CSs). DMD is a chronic, multi-systemic disease of debilitating muscle degeneration and weakness leading to progressive and severe long-term disability with large quality of life impacts on both patients and caregivers.7–9 There is no cure currently available for these patients. Traditional CSs such as prednisone and deflazacort are the current standard of care and can slow the progression of the disease.4,10 However, traditional CSs are associated with a series of adverse events (AEs) related to dose and treatment duration, and these adverse effects comprise a significant proportion of the overall burden of DMD. Shorter term AEs such as behavioural changes, weight gain and changes in physical appearance are burdensome and lead to dose reduction and

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	discontinuation of treatment.11–20 Longer term AEs such as progressive growth stunting leading to short stature for age, osteopenia and osteoporosis associated with bone fractures, cataracts or increased risk for diabetes mellitus, tend to be irreversible and also lead to dose reductions and treatment discontinuation.7,21,22 Dose reductions of traditional CS treatment due to tolerability results in reduced efficacy and leads to irreversible disease progression for patients, with treatment often being discontinued entirely.11–20,23,24 Vamorolone is a dissociative CS, combining the benefits of CSs25 with clinically relevant improvements of tolerability and safety. For instance, vamorolone treatment is associated with less severe and fewer behavioural issues compared to traditional CSs22,25,26, an absence of a growth stunting effect25 and reduced effects on bone health outcomes versus traditional CSs.25 It is important to note that there is an unmet medical need for anti-inflammatory treatments for DMD which do not have deleterious bone effects, as patients experience an increased risk of fractures both because of their disease and as a direct consequence of long-term CS use.27,28 This is supported by trial data (serum bone turnover markers were not impaired with vamorolone treatment versus prednisone and switching from prednisone to vamorolone resulted in a reversal of this bone turnover impairment25 and long-term safety data (reduced risk of any bone fracture for vamorolone patients versus patients receiving long term CS treatment (Appendix: Long term safety experience with vamorolone and indirect comparisons to standard of care)). It is acknowledged that there is some overlap in tolerability profile between vamorolone and traditional CSs, such as adrenal suppression, Cushingoid features, and weight gain. These can be detected by routine care and managed clinically by reducing the dose. These vamorolone dose reductions are expected to be associated with only a small nominal decrease in efficacy, which is unlikely to be clinically relevant for most patients (Appendix: Population Pharmacokinetic-Pharmacodynamic (PKPD) Analyses of Vamorolone Efficacy).
2	**Impact of and evidence supporting adverse events (draft guidance 3.7 and 3.11)** As acknowledged by the Committee and EAG, reduced AEs are the most significant advantage of treatment with vamorolone versus traditional CSs. AEs and long-term complications are the reason for traditional steroid switching, sub-optimal dosing and discontinuation. The improved AE profile of vamorolone enables long-term adherence to an efficacious dose, and thereby improves long term outcomes which accelerate disease progression, such as fractures. VISION-DMD was used to inform 24-week moderate and severe AEs in the model. However, additional analysis and long term safety data also support reduced incidence of AEs associated with vamorolone.[22,29] (Appendix: Effects of vamorolone versus prednisone and deflazacort – addendum to indirect comparison of safety; Appendix: Long term safety experience with vamorolone and indirect comparisons to standard of care): • **Weight gain and appearance**: Evidence from the long-term safety pool (VBP15-002 and VISION-DMD) shows that down-titration from 6mg to 4mg of vamorolone results in a reduction in risk of weight gain. A comparison of VISION-DMD and FOR-DMD 6-month data supports a reduction in incidence of Cushingoid features and skin/hair

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	changes compared to prednisone (Appendix: Effects of vamorolone versus prednisone and deflazacort – addendum to indirect comparison of safety). • **Growth stunting**: Vamorolone shows no risk for growth stunting compared to known long term irreversible risk for prednisone and deflazacort based on the vamorolone long term safety pool in comparison with FOR-DMD.[22,29] • **Behavioural issues**: A comparison of VISION-DMD and FOR-DMD 6-month data supports a reduction in behavioural issues (mild, moderate or severe) compared with prednisone and deflazacort (Appendix: Effects of vamorolone versus prednisone and deflazacort – addendum to indirect comparison of safety). • **Fractures**: The vamorolone long-term safety pool versus the long-term experience from CINRG shows an approximate [redacted] in risk of any bone fracture. This confirms the benefit on bone health, including reduction in risk of vertebral fractures for vamorolone compared with prednisone/deflazacort, from the comparison between FOR-DMD (36 months) and VBP15-LTE (30 months) (Appendix: Long term safety experience with vamorolone and indirect comparisons to standard of care). • **Cataracts**: There were no confirmed cases of cataracts for vamorolone across all trials. In contrast, there is a known increased risk for cataracts with both deflazacort and prednisone.[20] (Appendix: Long term safety experience with vamorolone and indirect comparisons to standard of care). • **Puberty**: Preliminary evidence suggests vamorolone may not affect the hypothalamus-pituitary-gonadal axis and therefore may not delay puberty as with traditional CSs (Appendix: Study VBP15-006, Steroid Switching Cohort Interim Report). • **Mineralocorticoid antagonism**: Vamorolone has shown an antagonistic effect on the mineralocorticoid receptor with a potency similar to that of eplerenone *in vitro* and in animal studies in contrast to the mild agonistic effect with prednisone or no effect with deflazacort.[30,31] This differential effect is expected to result in a reduced risk for hypertension with vamorolone in the long term and potential benefits on cardiac function similar to those observed with eplerenone, a treatment for cardiac complications in patients with DMD.[32] The Company agrees that accurate modelling of the tolerability of vamorolone and glucocorticoids is essential to capture accurately, given tolerability is a key clinical benefit for vamorolone. The model has therefore been updated to more appropriately capture the full burden of adverse events as well as the long-term implications of these: • In line with the committee's preference, the base case has been updated to include all AESIs from VISION-DMD[1]. The disutilities and resource use associated with mild AESIs used in the model are described in issues 8 and 9, respectively. At the point of submission, cataracts data were not available to include within the analysis, but have now been estimated via analysis of patient-level data from the CINRG registry. Kaplan-Meier (KM) data for prednisone and deflazacort with up to five years of follow-up were parametrised using the standard six curves in line with NICE Decision

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	Support Unit (DSU) Technical Support Document (TSD) 14. Data are provided in the accompanying Appendix for prednisone (Figure 15, Figure 17 and Table 19) and deflazacort (Figure 16, Figure 18 and Table 20), respectively. Clinical validation with three experts indicated that the rates of cataracts in clinical practice are low, and therefore the generalised gamma and exponential curves gave the most plausible outcomes for prednisone and deflazacort, respectively.[33] • The associated disutility and resource use assumptions for cataracts are described in issues 8 and 9 of this document. • As highlighted by the committee, VISION-DMD data are short-term, meaning it is hard to quantify long-term events from these data alone. Therefore, long-term data was sought for fractures, to address concerns over the long-term uncertainty of these events. Fracture rates were sourced from Joseph et al. 2019[2], a retrospective review of fractures over nine years in DMD patients receiving either daily or intermittent glucocorticoid regimes in the UK-based NorthStar Registry. KM data for prednisone and deflazacort were parametrised using the standard six curves in line with NICE TSD 14. Data are provided in the accompanying Appendix for prednisone (Figure 2, Figure 3, Figure 6, Figure 7, Table 5 and Table 6) and deflazacort (Figure 4, Figure 5, Figure 8, Figure 9, Table 7 and Table 8), respectively. Clinical validation with three experts indicated that the generalised gamma or log-normal, and log-normal or log-logistic curves gave the most plausible outcomes for daily and intermittent prednisone, respectively. This is based on their insights that between 50-60% of patients receiving daily prednisolone and 30-40% of patients receiving intermittent prednisolone would experience a fracture (vertebral or non-vertebral) by 15 years. For daily deflazacort, clinicians indicated that roughly 90% of patients would experience a fracture of any kind by the time they transition from paediatric to adult services, therefore, log-logistic was deemed the most plausible. The most reasonable curve for intermittent deflazacort was deemed to be either log-logistic or log-normal, based on clinical validation stating that 40-50% of patients would experience a fracture (vertebral or non-vertebral), however, a fracture rate higher than 75% at 25 years would be inappropriately high. Clinicians indicated that non-vertebral fracture rate is higher in ambulatory years, which will reduce when patients become non-ambulatory. Therefore, exponential would not be appropriate as exponential extrapolation only includes one hazard. Thus, due to the change in fracture rate hazard following loss of ambulation, exponential is not appropriate to use for any of the curve selections. • To calculate long-term vamorolone fracture rates, a HR was applied from a comparison of the fracture rate of daily prednisone and deflazacort from CINRG data relative to vamorolone long-term safety pool data, presented in Figure 12, Figure 13 and Table 11 of the Appendix. Given these changes, the model better encapsulates the full tolerability profiles of all treatments. • The adverse event data for deflazacort presented in the original company model was based on a naïve comparison of VISION-DMD (vamorolone) with FOR-DMD (deflazacort) given there is no head-to-head trial comparison of the two therapies. The frequency of adverse event measurement was lower in FOR-DMD than VISION-DMD (three months versus one month), resulting in lower incidences being captured

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	for deflazacort, thereby leading to a biased comparison in favour of deflazacort. Further, the incidence of cushingoid in FOR-DMD was focused only on those clinically relevant events from actively asking patients about cushingoid (then reported as AEs) while all actively capture events were reported as AEs in VISION-DMD independent of severity. The rates for deflazacort AEs were therefore modified based on further exploration of the FOR-DMD dataset and methodology to account for these differences in study design. Adjusted rates are presented in Table 1 of the Appendix. • The EAG asked for additional justification of the approach used to model adverse events. The Company maintains the methodology used, i.e. applying a QALY decrement to the incidence of AEs in the cycle they occur, is appropriate. In each model cycle, the per-cycle probability of events occurring (calculated from the rate of adverse events over the 24-week VISION-DMD period), was applied to the relevant proportion of patients to calculate the incidence of events. The company would likely to clarify therefore that the adverse events presented in the engine are not representative of the prevalence, but rather represent the incidence in that cycle. The total QALY loss per event (the disutility multiplied by the duration of the event) is then applied to the per-cycle incidence to capture the total QALY loss per event in the cycle the event occurs. It is possible that this approach causes a slight overestimation of the QALY loss due to discounting being applied in the cycle of event incidence however, any potential impact of this is expected to be extremely minor. • In line with committee preference to see equal impact of down-titration across treatment arms, the model has been updated to apply a decrease in AE rates when patients down-titrate from vamorolone 6mg/kg to 4mg/kg. The percentage decrease is aligned with the percentage decrease for patients who have down-titrated on steroids (82% of the full dose rate; Section B.3.3.3 of the CS). • A correction factor was applied to the application of AEs and spinal fusion surgery in the model. Following this correction, the Company believe that the model does not overestimate adverse events for the prednisone and deflazacort arms. In the latest model version, setting the vamorolone and prednisone/deflazacort arms to have equal rates of adverse events, disutilities and disease progression results in an equal QALY loss for each arm arising due to adverse events, thereby demonstrating that the AE are appropriately applied across treatment arms. Based on the updated model base-case and clinical evidence provided, vamorolone demonstrates a more tolerable treatment option within an effective dose range (i.e 4 to 6mg/kg) for DMD, both short and long-term.
3	**Differential effects of down-titration in efficacy and safety on vamorolone compared to standard of care (draft guidance 3.13)** The Company accept that there may be some impact on efficacy due to down-titration from 6mg/kg to 4mg/kg of vamorolone, however these are not expected to be clinically relevant for most patients, and therefore similar efficacy between the 4mg/kg and 6mg/kg doses of vamorolone is modelled in the updated base-case. Reduction of traditional CS doses has a greater relative impact on efficacy (and therefore risk-benefit profile) than dose reductions for vamarolone. Vamorolone has a positive risk-

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	benefit profile compared to placebo within the entire approved dose range. In contrast, traditional CSs have shown little efficacy benefit at reduced dose levels (required to achieve an acceptable safety and tolerability). Prednisone did not show a statistically significant improvement in efficacy versus placebo after 6 months at a reduced 0.3 mg/kg dose.[34] Analysis of the data from FOR-DMD confirms the increased risk of losing efficacy in patients who need to reduce CS recommended doses due to safety and tolerability. Two years after reducing the dose, a two-fold increased risk ([redacted] ([redacted]) for losing the ability to stand is observed in patients who had to reduce the dose of daily prednisone or deflazacort due to side effects in the first 12 months, compared with patients who could maintain the recommended dose at least 12 months. Consistent results for an accelerated progression were observed in the change from baseline in time to stand and 6-minute walk distance, or their time to return to baseline for standard CS patients reducing their dose. Further confirmation of a correlation between reduced long-term efficacy and reductions in the dose of CSs have been observed in multiple natural history data (Appendix: Long term dosing experience of with standard of care corticosteroids). Reducing vamarolone dose from 6mg/kg to 4 mg/kg still retains a strong positive risk-benefit profile and offers an efficacious lower dose as an alternative for patients who might experience safety and tolerability issues at the starting dose. Vamorolone 6 mg/kg has shown a benefit over CS at recommended doses (similar efficacy benefit, reduced safety and tolerability risk). [redacted] (Appendix: Population Pharmacokinetic-Pharmacodynamic (PKPD) Analyses of Vamorolone Efficacy)), whilst further improving safety and tolerability.[34] (Appendix: Population Pharmacokinetic-Pharmacodynamic (PKPD) Analyses of Vamorolone Efficacy) As a result, the model has been updated with functionality to address the EAG's request, though this is not considered in the base case. Model users can modify the efficacy of vamorolone down-titrated patients, taken as an average of the transition probabilities of those on full dosing and those off treatment, as per the original CS. A scenario analysis is presented using a reduced efficacy by 7% for vamorolone 4mg/kg versus vamorolone 6mg/kg, chosen as the [redacted]) (Appendix: Population Pharmacokinetic-Pharmacodynamic (PKPD) Analyses of Vamorolone Efficacy). In the original CS, the efficacy of down-titrated steroids was based on clinical opinion. To increase the validity of the model assumptions, patient-level data for TTSTAND in FOR-DMD were analysed. The HR of [redacted] was implemented in the model to capture the increased speed of disease progression for down titrated patients. In line with the committee's suggestion, functionality has been added for vamorolone down-titrated patients, although the base case assumes an HR of 1 in line with the available PKPD data. It is important to note that down titration has implications on the rate of adverse events in the model, not only efficacy, so does not solely benefit the vamorolone arm.
4	**Discontinuation extrapolation (draft guidance 3.12)** In the company model, following clarification questions, the proportion of patients on vamorolone and CSs were estimated by fitting independent parametric curves to each treatment arm. The data source for each treatment included VISION-DMD for vamorolone, CINRG data for deflazacort and prednisone, and with a log-logistic selected for all curves

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	as the company base case. These curves are shown in the clarification response document, Figure 7 and Figure 8, respectively. The EAG's preferred assumption was the proportion of patients discontinuing vamorolone being equal to CINRG data for deflazacort in the long-term, whilst also opting for a generalised gamma curve due to this aligning more closely with prednisone and deflazacort KM data. In the ACD, the committee consider the EAG's assumptions preferable, while noting uncertainty. Given there are no alternative long-term vamorolone discontinuation data available, the company have aligned with the EAG's preferred assumptions. As such, in the updated base case, the discontinuation of vamorolone is aligned to the deflazacort CINRG data, with generalised gamma as the selected extrapolation curve. This represents the highest estimate of long-term retention on treatment of all parametric curves tested, therefore the company consider this a conservative estimate.
5	**Efficacy of vamorolone compared to prednisone (draft guidance 3.6 and 3.10)** The Company does not agree with the Committee's conclusion concerning improvements across all muscle function outcomes. The draft guidance specifies that although vamorolone improves outcomes compared with placebo, the Committee did not believe that there was any robust evidence to support the conclusion that vamorolone is equivalent to prednisone, or deflazacort. The Committee considered that modelling based on an assumption of equivalent efficacy was not reliable and that vamorolone might result in slightly worse muscle function outcomes and overall disease progression versus prednisone. Vamorolone has been shown to be an effective and safe treatment for DMD and is associated with decreased AEs compared with CS in the long term.[35] These results were similarly demonstrated in the short term over a 24-week treatment period in the VISION-DMD trial.[1] Expert opinion is that the numerical difference observed in VISION-DMD is not likely to be clinically relevant. However, in a real-world setting, a vast majority of patients are not able to tolerate recommended doses of prednisone or deflazacort whereas long term data with vamorolone indicate most patients on vamorolone are able to tolerate a higher effective dose range due to its improved safety and tolerability profile. The company would like to address the Committee's concerns on evidence suggesting the equal equivalency of vamorolone to prednisone and likewise comment on the discussions surrounding the numerical differences in muscle function outcomes in the VISION-DMD trial. Concerning vamorolone's similar equivalence to prednisone, in responses collated from key opinion leaders (KOL) in a Delphi panel, KOLs agreed that "adherence to optimal dose vamorolone and glucocorticoids would yield similar efficacy, and that despite prednisone showing numerical, and some statistically significant improvements in muscle function, the primary outcomes of VISION-DMD could still be used to suggest comparable efficacy for vamorolone and prednisone."[36] KOLs also agreed that it was reasonable to assume that the long-term trajectory for those with DMD would be similar if they were on vamorolone or prednisone.[36] The experience from natural history studies of traditional CSs shows that dose-reductions from recommended dose start early (within 12 months of treatment initiation), and most patients will be using reduced doses of CS by the time they are close to losing ambulation

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	(Appendix: Long term dosing experience of with standard of care corticosteroids). The use of reduced doses versus recommended/optimal dose leads meaningfully reduced efficacy for traditional CSs.[28, 34,37,38] The improved risk-benefit profile of vamorolone with a reduction of damaging side effects in the short and long term compared to prednisone or deflazacort is expected to improve compliance and allow patients to maintain treatment at efficacious doses. The long term experience of patients with DMD treated with vamorolone in the UK shows that after more than 4 years of treatment, most of the patients (25 out of 27) are still being treated with vamorolone 6 mg/kg or 4 mg/kg (Appendix: Long term dosing experience in the UK). The experience of the long-term safety vamorolone pool confirms the experience from the UK with a majority (~80%) of patients receiving vamorolone 6 mg/kg or 4 mg/kg after an average of 4.4 years of treatment, and up to 6 years (Appendix: Long term safety experience with vamorolone and indirect comparisons to standard of care). Likewise, the improved safety and tolerability profile of vamorolone compared to prednisone ensures patients adhere to treatment and receive full benefits of the intervention over the long term. Statements collected as part of the patient expert statements and available in the Committee Papers, demonstrate that the negative side effects of CSs were so critical that for people with DMD and their caregivers, they outweigh a very small and hypothetical reduction in efficacy for vamorolone versus prednisone and deflazacort.[39] *"As the boys deteriorate anyway, we start to see less benefit and only increased side effects risk. If a treatment has a reduced efficacy but also reduce risk, as parents we will be happier to carry on treatment longer rather than curtail treatment."* *"I will take an improved safety profile over improved muscle function any day of the week."* *"An improved safety profile is of the utmost importance to me. My son's growth and behavioural issues have been huge sources of concern; I'd take improvement in safety profile over muscle function outcomes, especially if unwanted problematic side effects were reduced/eliminated."* *"It would depend how much worse the efficacy was. If it was marginal or a small difference, vamorolone would still be my preferred treatment."* *"I think I would rather have that than all the side effects from steroids we are now dealing with."* *"In our instance, a slightly reduced efficacy but better safety profile would be an acceptable balance; if the efficacy was significantly worse than CS equivalents then it would tip the balance and become an unviable option."* The Company stands by the judgement of UK clinical experts, that there is no clinically meaningful difference in efficacy between vamorolone 6 mg/kg and prednisone or deflazacort used at recommended doses and would like to address concerns relating to numerical differences in muscle function outcomes.

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	The experience of assessing efficacy across traditional CSs in DMD highlights the risks of interpretations based on numerical but not statistically significant or clinically relevant differences within and across studies. For traditional large clinical studies, randomisation will produce balanced patient groups, but in rare disease, with small sample sizes there is a high chance of imbalance in terms of potential prognostic factors. This needs to be adjusted for in statistical analysis, however, statistical modelling is not designed to adjust for numerical differences due to baseline covariates; however, these should be considered when assessing statistical significance. In the VISION-DMD trial, there was no statistical difference in the efficacy after 6 months with prednisone or vamorolone 6 mg/kg despite imbalances in anthropometric and motor function between arms, biasing results in favour of prednisone.[1] This finding was also robust to adjustment for imbalances at baseline between the groups. Numerical differences observed at baseline and on apparent treatment effects between vamorolone 6 mg/kg and prednisone in the VISION-DMD study are within the variability expected for studies of this sample size in this heterogeneous population. DMD is a chronic, multi-systemic, heterogeneous disease where patients progress at different ages and at different speeds. The probability of seeing an improvement in functional outcomes in patients with DMD depends on the level of disability at the time they start treatment. A more advanced population as observed on the vamorolone 6 mg/kg arm compared to the prednisone or placebo study arms, will have a lower likelihood of showing an improvement after starting treatment, as supported by subgroup analysis of the VISION-DMD study.[1] Therefore, imbalances at baseline despite randomisation are to be expected in studies with small sample sizes typical for clinical trials in the DMD population. Variability within and between clinical trials assessing the efficacy of traditional CSs can be clearly seen in past efficacy evaluations of prednisone: • Mendell et al., 1989[40], showed a 40% reduction (-2.9 seconds) from baseline in the time to stand after 6 months of treatment with prednisone 0.75 mg/kg.[40] • Griggs et al., 1991[37], in an almost identical study with a similar population showed that the reduction from baseline in time to stand was approximately half of what was observed previously by Mendell[40], i.e. only 22% reduction (-1.92 seconds).[37] • Griggs et al., 2016[10] was the pivotal study for deflazacort but also included a prednisone 0.75 mg/kg arm and a population similar to the first two studies (age ~9 years old, time to stand approximately 8 seconds at baseline) and showed a 24% reduction (but an even smaller numerical change from baseline of -1.68 seconds).[10] In summary, the efficacy of prednisone in terms of numerical improvement from baseline almost doubled between clinical trials within the same population type. This highlights the known disease heterogeneity of DMD that cannot be fully mitigated in clinical trials of the sample size typically seen in rare diseases. Likewise, numerical differences within studies in this population should be interpreted with caution. In the pivotal study of deflazacort the efficacy of prednisone was numerically but not statistically significantly lower than that of deflazacort.[10] This supported the interpretation that deflazacort was a more efficacious treatment compared to prednisone in DMD. However, this interpretation was not confirmed

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	in subsequent studies designed to test this hypothesis, for example FOR-DMD, thus highlighting the risks of making interpretations on numerically but not statistically significant differences in studies of the typical DMD sample sizes.[22] Numerical differences that were not clinically relevant were also observed between the prednisone arms of VISION-DMD and FOR-DMD. For example, the change from baseline to week 24 for the 6-minute walk test in the matched comparison was 15 meters higher for the prednisone arm in FOR-DMD when compared to the prednisone arm of VISION-DMD.[1, 22,41] In conclusion, interpretations on differences between treatment arms in clinical trials should be based on pre-defined statistical analysis for which the study was adequately designed. Numerical differences without statistical significance should not be used for interpretation. To further address concerns from the committee, the company have provided a cost-effectiveness scenario in which vamorolone 6mg/kg was assumed to have lower efficacy than prednisone 0.75mg/kg and deflazacort 0.9mg/kg. To test this, reductions of 5% and 10% versus each steroid were considered as scenarios. In both cases, this only had a minor change on the ICER, as shown in Table 47 of the accompanying economic appendix. In addition, a scenario assuming a reduced efficacy for vamorolone 4mg versus vamorolone 6mg was also implemented, with a hazard ratio of 1.075. This also leads to a very minor change in the ICER, as shown in Table 47 of the accompanying economic appendix.
6	**Position of vamorolone in CS-naïve and experienced patients (draft guidance 3.4 and 3.5)** The Company agree with the Committee's conclusion that vamorolone has benefits in CS-naïve patients. Vamorolone will also benefit patients who have had or are receiving traditional CSs and are unable to tolerate the side effects or wish to avoid the long-term irreversible consequences of CSs such as growth stunting and osteopenia. Patients can be switched from traditional CSs to vamorolone without the need for treatment interruption or dose reduction as per the vamorolone Summary of Product Characteristics (SmPC). Patients previously treated on a chronic basis with traditional CSs should switch to vamorolone 6mg/kg to minimise the risk of adrenal crisis. Given that vamorolone exposure is within the established therapeutic range and switching to vamorolone from prednisone or deflazacort has been shown to be well tolerated, there is no clinical reason to believe that any patients previously treated with traditional CS would not benefit from treatment with vamorolone, as evidenced by the 004 and VBP15-006 studies. Evidence from VISION-DMD suggests that switching from 0.75mg/kg of prednisone to 6mg/kg of vamorolone after 24 weeks results in retaining benefit in motor function endpoints. Of relevance is the recovery of growth trajectory in patients switching from prednisone 0.75 mg/kg to vamorolone, as seen in the increase in mean and median height z-scores between week 24 and week 48. Behavioural problems were stable after switching from prednisone to vamorolone, as no increase in behavioural problems were observed after starting vamorolone. Also, no increased weight gain and no increase in Cushingoid appearance were reported after switching.

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	Experience in switching from CS treatment to vamorolone comes from the fully recruited but still ongoing VBP15-006 study (Appendix: Study VBP15-006, Steroid Switching Cohort Interim Report). In this study, 22 patients aged >7 to 8 years old previously receiving CS were switched to vamorolone 2 mg/kg or 6 mg/kg without interruption or dose-titration. Symptoms suggestive of adrenal insufficiency were reported in two patients with pre-existing adrenal suppression and switching to the 2 mg/kg dose, which were resolved by supplementing the 2 mg/kg vamorolone dose with hydrocortisone. No patient switching from long-term CS developed any symptoms suggesting adrenal insufficiency after switching to vamorolone 6 mg/kg, including those patients with pre-existing adrenal suppression. This data confirmed the recommendation of switching from CS to vamorolone 6 mg/kg without interruption or tapering. As discussed and acknowledged by the Committee and EAG in their draft guidance, the safety and tolerability profile of traditional CS treatment is inadequate. The Company would like to emphasise the unmet need in the population treated with traditional CSs and the potential benefit of vamorolone in CS pre-treated as well as naïve patients.
7	**Overestimation of survival (draft guidance 3.9)** The Committee noted that the median survival expected for people with DMD from the literature is around 30 years, however, the natural history model predicted a greater life expectancy than this. Clinical experts further expressed, and the Committee subsequently concluded that the model may have overestimated life expectancy for DMD. The Company believes that the life expectancy predicted by the economic model is in line with the life expectancy reported in the literature for DMD patients (range: 21.0 to 36.2 years, median: 29.9).[42] Further, the model used was developed by Project HERCULES, a multinational collaboration set up by Duchenne UK to develop tools and evidence to support Health Technology Assessments and reimbursement decisions for new treatments for DMD, which NICE participated in. The 'kink' seen in the mortality curve was due to an adjustment made to the original Project HERCULES model. When calculating the transition probabilities for the natural history model, the transitions resulted in largely unrealistic survival estimates with patients remaining in HS 8 for extended periods of time. To account for this, a piece-wise exponential extrapolation was applied with an increased rate of mortality beyond this point, leading to the 'kink' in the health state curve. To generate more plausible survival estimates, and address concerns from the Committee regarding a potential overestimation of survival compared with clinical practice in the economic model, the company have utilised published KM data from Broomfield et al. 2021[3], which presents survival probabilities of DMD patients split by birth cohort. As the most recent cohort, and one which most closely matched median survival in the literature, the post-1990 cohort was selected. These curves were digitized and extrapolated, using the six standard parametric curves in line with TSD 14 (Figure 21, and Table 22 of the economic Appendix). The generalised gamma provided the best statistical and visual fit to the data, and was applied within the model as a per-cycle mortality risk. Mortality risk per-cycle was set to match the highest per-cycle risk of mortality out of the natural history data, the NHM, or the Broomfield data. The resulting median survival estimates in the updated

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	model are in line with the life expectancy range cited by Landfeldt et al 2020[42], with median treatment ranging from 25.02 years for prednisone to 26.43 years for vamorolone depending on the treatment arm. A longer time horizon of 95 years was also chosen for the revised base case to capture the small proportion of patients (15%) who are still alive at the end of the 50-year time horizon.
8	**Health-state utilities and adverse event utilities (draft guidance 3.14 and 3.15)** The number of caregivers has been updated within the model to reflect a more granular approach. In the updated base case, 1 caregiver has been applied to all ambulatory health states (1-3), and 2 caregivers have been applied to all non-ambulatory health states (4-8) to reflect the increased caregiver burden and requirements once a patient loses ambulation. The face validity of the application of adverse events disutilities was queried by the Committee; specifically, the application of behavioural disutility. The modelling method for adverse events has been extensively checked by an external modelling expert who gave approval on the application. The application of behavioural issues for the duration of 6 months was initially validated through clinical expert opinion, which the EAG did not find unreasonable. Clinical opinion from three UK experts gathered to inform the Company's response to the ACD indicated that steroid-induced behavioural issues may last up to one to two years; therefore, the company has updated its base case to 18 months.[33] Given feedback from the EAG and further validation with clinical experts, it was deemed appropriate to adjust some of the disutilities associated with adverse events and health states. The following changes were made for the updated base case: • Landfeldt et al., 2023[6] health states utilities were applied. Utilities were measured by self or caregiver proxy, depending on the age and cognitive ability of the patient using EQ-5D-3L, whereas other source only relied on proxy measurements and other quality of life instruments. Additionally, Landfeldt et al. 2023[6] included the largest UK patient sample size and was accepted in the recent NICE appraisal for Ataluren in DMD[6]. Therefore, the Company believes that this is the most appropriate source, with Evans et al., 2020[43] (BoI study) explored in a scenario analysis. • Clinical experts advised that growth stunting and its utility impact is lifelong. The disutility has therefore been applied for an increased duration of 8 years instead of one year (as reported in NICE HST 14[44]); the eight-year duration may still be considered conservative, due to patients experiencing growth stunting from treatment initiation (age 4) and would experience the negative repercussions for a life-time, and at a minimum until loss of ambulation (average loss of ambulation 11.2 years for daily prednisone and 13.9 for daily deflazacort).[8] Furthermore, this disutility cannot be assumed to be captured within the health state utilities alone since it is treatment specific, and therefore would vary based on the rate of stunted growth occurring for each treatment. A scenario analysis with an increased duration 20 years to reflect the lifelong impact of growth stunting is also presented. • In the first committee meeting, clinical experts advised that fractures may lead to loss of ambulation, which was not previously included in the economic model. Yildiz et al 2020[45] reported that 36.4% of those with a long bone fracture lost ambulation permanently. In the updated model, this proportion is applied to the fracture rate for

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	ambulatory health states to calculate the proportion with a fracture moving to the first non-ambulatory health state (health state 4). • The disutility has been increased for spinal surgery. Bridwell et al.1999[46] identified that patients with DMD often lost hand function due to spinal surgery. Thirteen of 29 patients following spinal surgery were unable to feed themselves with five of them being unable to do so due the increased distance from hand to mouth from the spinal surgery, functionality that patients never regain. Clinical opinion states that this life-long impact remains uncaptured in the model. Disutility associated with sacrum joints and back pain as a result of spinal surgery, an additional QALY loss arising from spinal surgery, is also not appropriately captured in the model. Therefore, increasing the duration of this adverse event to 2 years, is still considered a conservative estimate. • A disutility associated with cataracts was added, using a cataract disutility value from HST11[47] for inherited retinal dystrophies caused by RPE65 gene mutations (mean patient aged 15 years). A disutility value of 0.142 was applied for one month as a one-off QALY loss per cataract event. Clinical expert opinion deemed a one-month duration to be appropriate, due to the short-term nature of cataracts. • As the updated base case considers all adverse events, disutilities were required for mild events. Due to a paucity of data, these were set to 25% of the disutilities arising from moderate to severe events. The model applies a disutility for carers for behavioural issues of 18-months[33]. The duration of the event was informed by clinical expert opinion, which advised that while complex behavioural issues such as autism are experienced for a lifetime, mood-related behavioural issues arising from treatment would last between one to two years. Therefore, the company consider an 18-month duration appropriate and even conservative.
9	**Resource use and costs (draft guidance 3.16)** Given feedback from the EAG and further insights gathered from clinical experts it was deemed appropriate to adjust the costs associated with adverse events and health states. The following changes were made: • Growth hormone treatment costs for growth stunting were removed in line with the Committee's preference. Clinical validation advised that appropriate resource use associated with stunted growth would be two consultant led outpatient endocrinologist visits based on costing from NHS reference cost 2021/22 using codes WF01B for 'First attendance, single professional.' and 'WF01A Follow-up attendance - single professional'.[48] • A cost for cataracts was added based on clinical validation, using a weighted average of NHS reference costs 2021/22 for intermediate to complex surgery. Clinical validation stated that paediatric DMD patients would have complex needs and cataracts procedures would incur higher costs than typical elective cataract procedures; therefore, minor cataracts procedure costs were excluded from the calculation. The weighted average of elective inpatient code was used; complex cataract or lens procedure, with CC Score 2+ (BZ30A), CC score 0-1 (BZ30B), very major cataract or lens procedure, with CC Score 2+ (BZ31A, with CC score 0-1 (BZ31B), intermediate cataract or lens procedure, with CC score 2+ (BZ32A), or CC score 0-1 (BZ32B).[48]

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	• Skin/hair change moderate-to-severe event resource use was updated based on clinical validation to include one paediatric consultant led dermatologist outpatient appointment using NHS Reference costs 2021/22 WF01B code.[48] • The fracture costs for 'non vertebral' fractures were updated based on clinical validation, to reflect the weighted average of the most severe NHS reference cost fractures (using codes HE51D, HE51E, HE51A, HE41A, HE31D, HE21E, HE21B, HE11F, HE11E, HE11C, HE11D, HE31E, HE11G).[48] This is in line with clinical expert opinion to reflect the difficulties associated with surgery for DMD patients. • Bisphosphonates costs associated with fractures were updated in line with Joseph et al 20192, whereby 63% of patients received bisphosphonate treatment, of which 69% received oral and 31% received IV per treatment arm. IV bisphosphonate costs are only applied to non-vertebral fractures and oral bisphosphonates are used for vertebral fracture. The cost per IV was also updated in line with clinical expert opinion as the previous resource use cost of blood transfusion, or chemotherapy was deemed an inappropriate proxy. In place of this, 'Regular Day Admission, Continuous Infusion of Therapeutic Substance for Pain Management' currency code 'AB18Z' was used, which clinicians confirmed to be most appropriate.[48] The average dose of prednisone or deflazacort was updated based on the long-term average dose used for each age in the CINRG data set (Appendix: Long term dosing experience of with standard of care corticosteroids). The costs for prednisone and deflazacort were then calculated for the respective dose per cycle of the regimen used. • A cost for weight gain and behavioural issues for mild AEs, was applied. For weight gain, clinical expert opinion indicated that one dietitian appointment would be appropriate. For behavioural issues, referral to community paediatrician before receiving therapy session was added. NHS reference costs 2021/2022 'HCC02 Common mental health problems 'low severity with greater need' was used.[48] The remainder of mild AEs are assumed to be captured within the patients routine care with neuromuscular specialists. • The source of health state costs was updated to the Landfeldt et al., 2017[5] publication, as it was used in the NICE appraisal for ataluren in DMD and no issues were raised.[6] Although surgery costs were not captured in Landfeldt et al., the surgery cost for cataracts is now captured as part of the treatment for adverse events, following NHS reference costs 2021/22.[48]
10	**Severity modifier (draft guidance 3.17)** The Company agree with the Committee's conclusion that a severity weight of 1.7 is appropriate. DMD is a condition with a high degree of severity, as reiterated by the Committee and ERG, clinical expert opinion, and broader stakeholder engagement, with limited survival and a high burden on both patients and caregivers. The updated model provided with this response demonstrates that the appropriate use of Landfeldt et al. 2023[6] results firmly within the criteria for receiving a 1.7 severity weighting, and has been applied in line with the EAG's correction to patients QALYs only and not caregivers. The final model ICER is inclusive of this as part of its corrected base case.
11	**Managed access** The Company would welcome discussion for entering a managed access agreement, in line in the proposal submitted on 3rd April 2024, if the Committee does not recommend

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	vamorolone for routine commissioning, in order to ensure that patients in England and Wales can access vamorolone as quickly as possible
12	**Revised base case** The revised base case includes a fully incremental analysis by comparing vamorolone with both prednisone and deflazacort. The updated model includes the following amendments to its base case assumptions: • Vamorolone discontinuation is in line with deflazacort CINRG data, utilizing a generalised gamma curve. • Mortality estimates are in line with Broomfield et al.(2021)[3] in line with the EAG recommendation. • Efficacy of patients who down-titrate on prednisone and deflazacort aligned to HR based on the CINRG data. • Efficacy for patients on no treatment aligned all health states to McDonalds et al. (2018)[4] 2.41 value. • AE rates for patients who down-titrate on any treatment all set to 82% reduction from full dose AE's. • A stopping rule has been implemented, with all patients receiving vamorolone until nighttime ventilation, following which no costs or benefits are applied to vamorolone patients. • Discontinuation for vamorolone set equal to deflazacort CINRG data with a generalised gamma curve. • Out of scope costs were excluded in line with the EAG recommendation. • Health state costs are in line with the Landfeldt et al 2017.[5] • Growth hormone costs set to two endocrinologist visits per event in place of hormonal therapy costs for stunted growth. • Growth stunting disutility increased to a duration of 8 years. • Behavioural issues disutility increased to 18 months. • Two caregivers assumed from loss of ambulation until death. • The number of patients receiving spinal surgery is based on cumulative loss of ambulation and discontinuation. • Patients may lose ambulation due to the occurrence of a long bone fracture. • Bisphosphonates costs refined in line with Joseph et al. (2019)[2] to reflect real-world clinical practice. • Cataracts included with associated costs and disutilities (1 month disutility) • Average dose amended in line with average dose by age based on CINRG for prednisone and deflazacort. The updated base case ICER is shown in Table 38 in the economic Appendix of new evidence.

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Vamorolone for treating Duchenne muscular dystrophy [ID4024]

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Vamorolone for treating Duchenne muscular dystrophy [ID4024]

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New evidence

Adverse events

Table 1: Deflazacort (90 mg/kg) modified AE data based on FOR-DMD

	AEs of all severity	Moderate to severe AEs	Mild AEs
Weight gain	[redacted]	[redacted]	[redacted]
Behaviour issues	[redacted]	[redacted]	[redacted]
Cushingoid	[redacted]	[redacted]	[redacted]
Infections	[redacted]	[redacted]	[redacted]
GI symptoms	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]
Skin/Hair changes	[redacted]	[redacted]	[redacted]

Abbreviations: AE – Adverse event; GI – Gastrointestinal; kg – Kilogram; mg – Milligram.
Source: Data not published. Original source for FOR-DMD: Guglieri et al. (2022).[1]

Table 2: Mild AESI data - VISION-DMD data

	Vamorolone 6mg	Prednisone 0.75mg/kg	Placebo
Weight gain	17.86%	6.45%	6.90%
Behavioural issues	21.43%	6.45%	10.34%
Cushingoid effects	25.00%	22.58%	0.00%
Immune supressed/infection	32.14%	25.81%	34.48%
GI symptoms	28.57%	22.58%	24.14%
Diabetes	3.57%	9.68%	3.45%
Skin/Hair change	3.57%	9.68%	6.90%

Abbreviations: AESI - Adverse event of special interest; GI – Gastrointestinal; mg – Milligram.
Source: Data not published. Original source for FOR-DMD: Guglieri et al. (2022)[1]

Table 3: Vamorolone 4mg AESI – Application of 82% reduction (SoC weighted average reduction)

	Vamorolone 4mg - moderate/severe	Vamorolone 4mg - mild
Weight gain	[redacted]	[redacted]
Behavioural issues	[redacted]	[redacted]
Cushingoid effects	[redacted]	[redacted]
Immune supressed/infection	[redacted]	[redacted]
GI symptoms	[redacted]	[redacted]

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	Vamorolone 4mg - moderate/severe	Vamorolone 4mg - mild
Diabetes	[redacted]	[redacted]
Skin/Hair change	[redacted]	[redacted]

Note: 82% in line with the average SoC reduction in daily to intermittent prednisone from FOR-DMD.
Abbreviations: AESI – Adverse event of special interest; GI – Gastrointestinal; mg – Milligram; SoC – Standard of care.
Source: Data not published. Original source for FOR-DMD: Guglieri et al. (2022).[2]

Figure 1: Hazard ratios taken from FOR-DMD study – time to lose stand by dose reduction

Abbreviations: N – No; Y – Yes.
Source: Data not published. Original source for FOR-DMD: Guglieri et al. (2022).[2]

Down titration

Table 4: Efficacy hazard ratio applied from FOR-DMD for down titrated patients receiving standard of care

Description	Hazard Ratio	Lower	Upper
First year dose reduction yes vs no	[redacted]	[redacted]	[redacted]

Source: Data not published. Original source for FOR-DMD: Guglieri et al. (2022).[2]

Table 5: Average down-titrated dose and cost by treatment arm

Average dose by age treatment arm			Prednisone: cost per one month per /kg	Deflazacort: cost per one month per /kg
Age (years)	**Deflazacort**	**Prednisone**		
4.10	0.80	0.68	£0.72	£0.00

Source: Birnkrant et al. (2018)[3], Bello et al. (2015).[4]
Note: Based on average down titration of 25-33% as reported in Birnkrant et al. (2018).[3]
The economic model accounts for down titration and cost per month by age, table illustrates cost for start age.
Dosing in line with the average dose of daily prednisone and deflazacort in Bello 2015 (75% prednisolone and 83% deflazacort).

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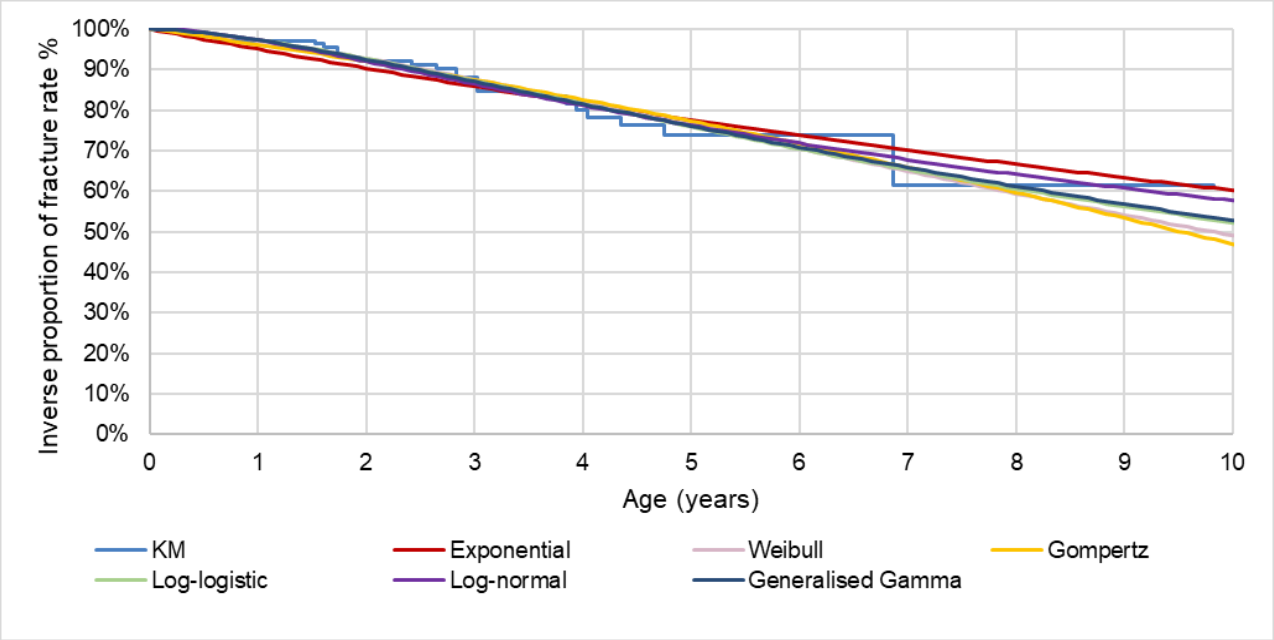
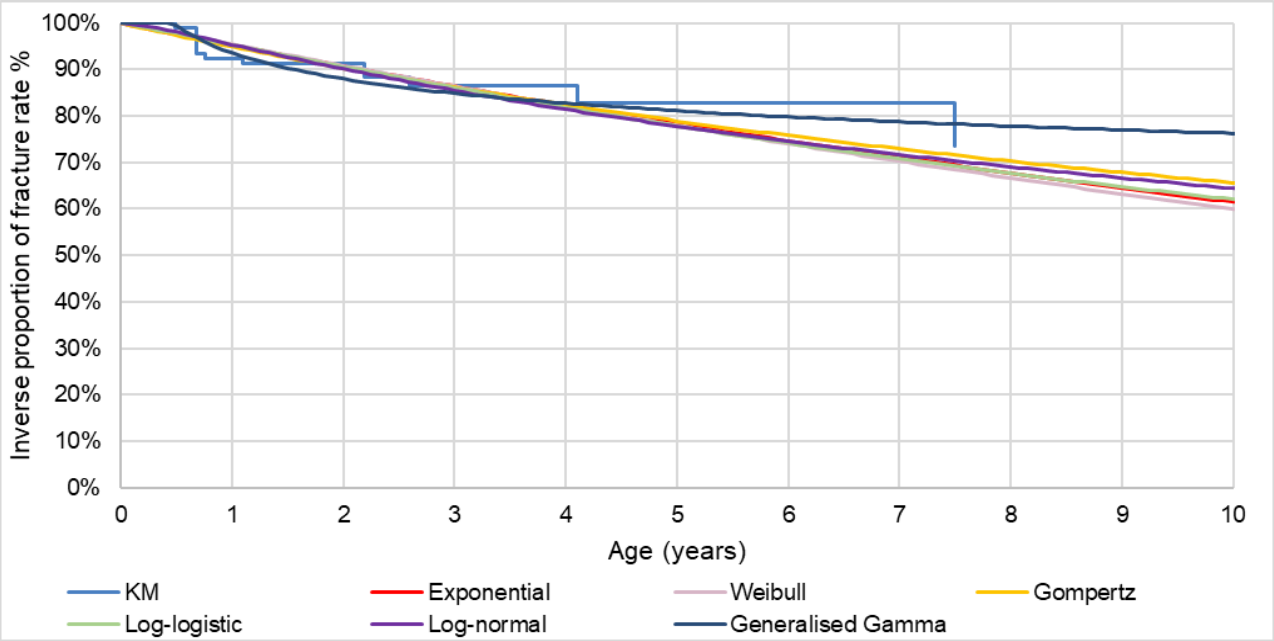
Adverse events - fractures

Figure 2: Joseph et al. (2019) – Daily prednisolone: all fractures short-term



Abbreviations: KM – Kaplan Meier.
Source: Joseph et al. (2019).[5]

Figure 3: Joseph et al. (2019) – Intermittent prednisolone one: all fractures short-term



Abbreviations: KM – Kaplan Meier.
Source: Joseph et al. (2019).[5]

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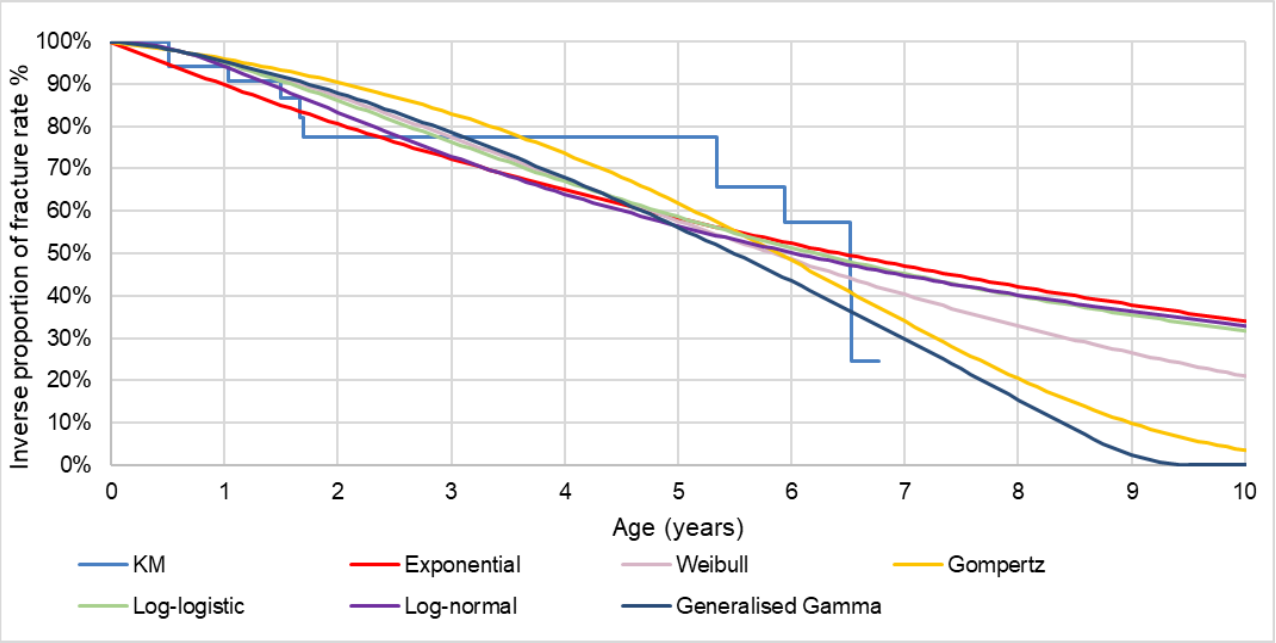
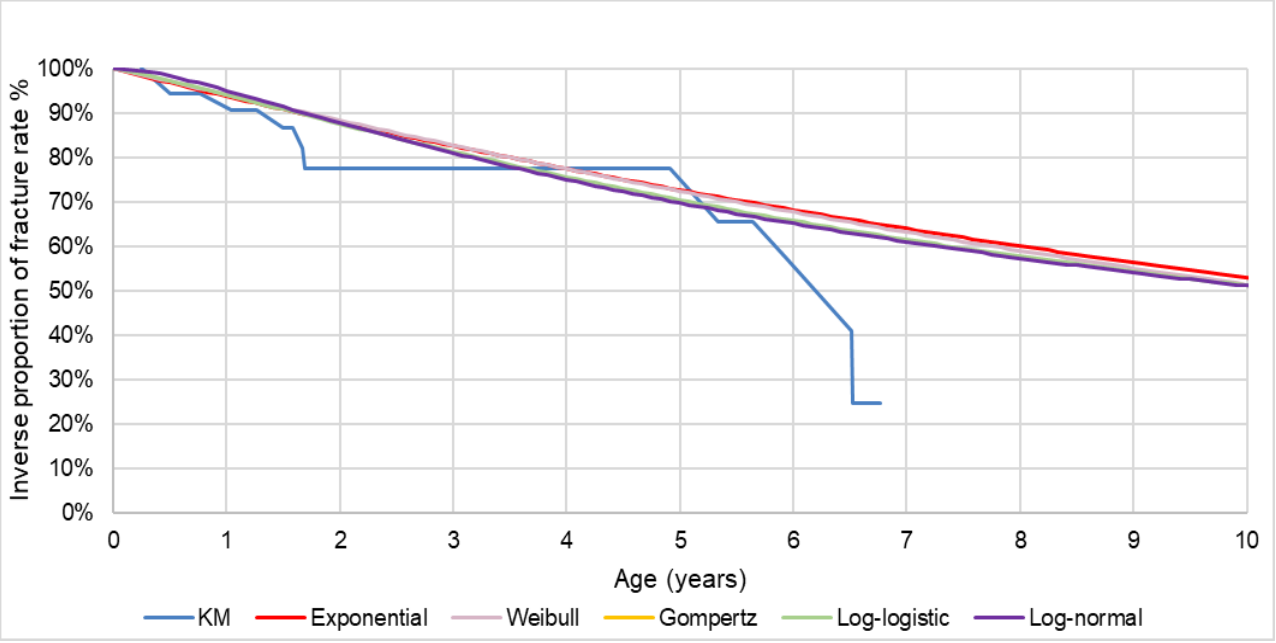
Figure 4: Joseph et al. (2019) – Daily deflazacort: all fractures short-term



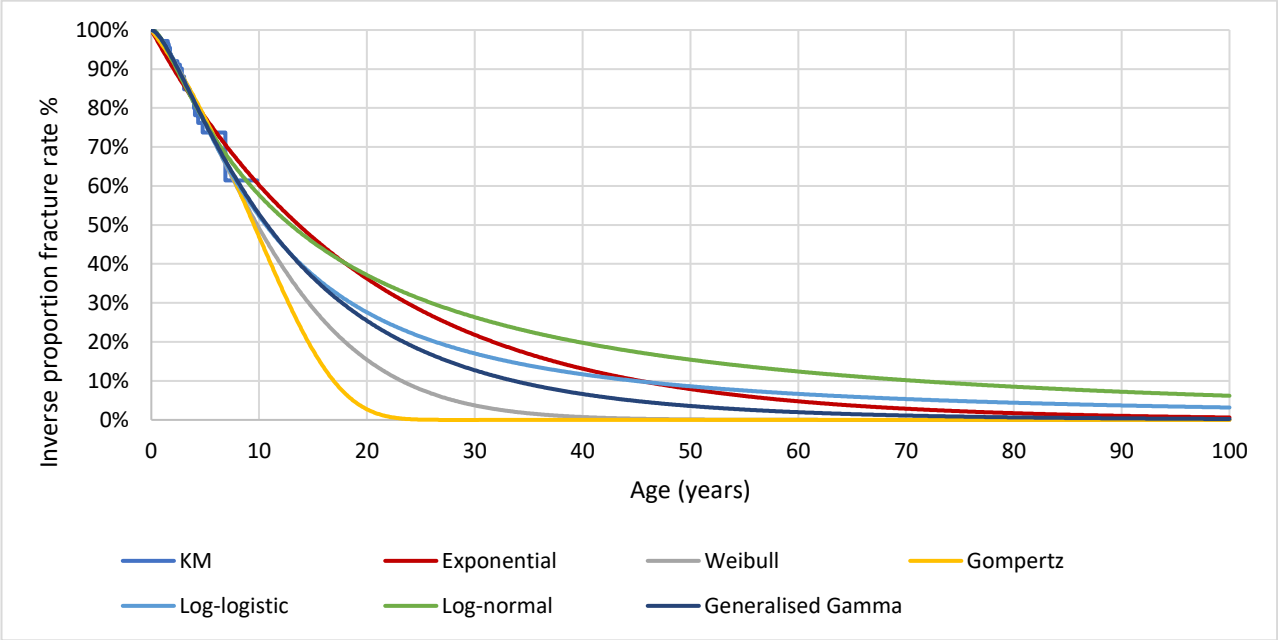
Abbreviations: KM – Kaplan Meier.
Source: Joseph et al. (2019).[5]

Figure 5: Joseph et al. (2019) – Intermittent deflazacort: all fractures short-term



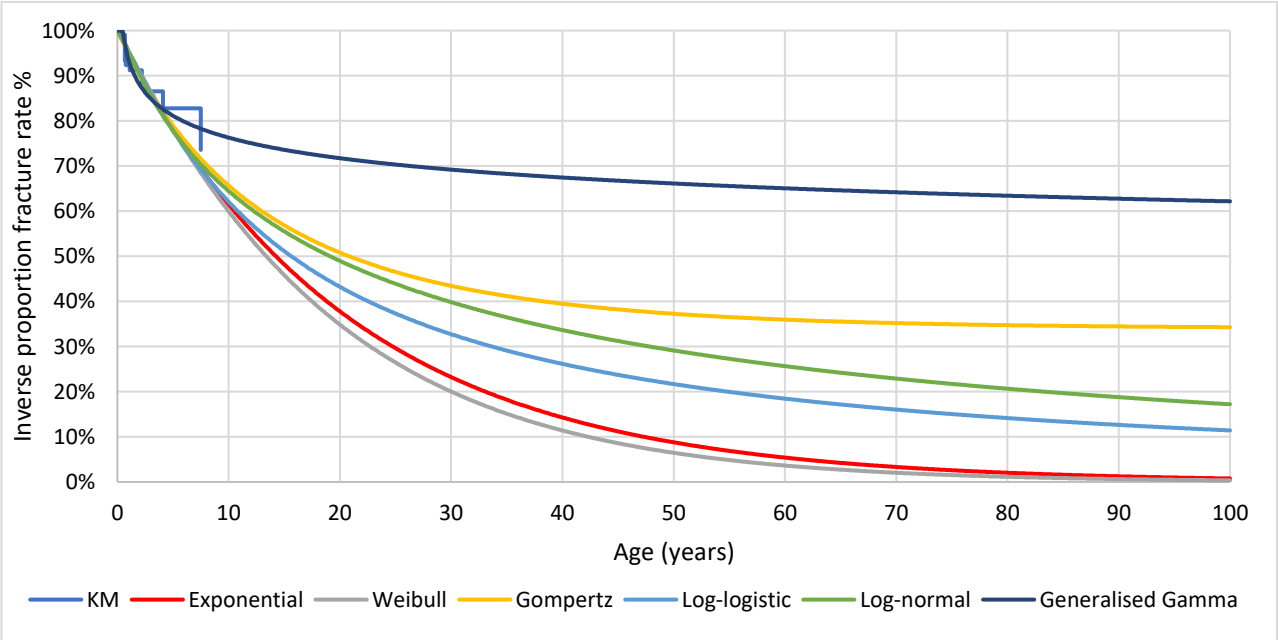
Abbreviations: KM – Kaplan Meier.
Source: Joseph et al. (2019).[5]

Figure 6: Joseph et al. (2019) – Daily prednisolone: all fractures long-term



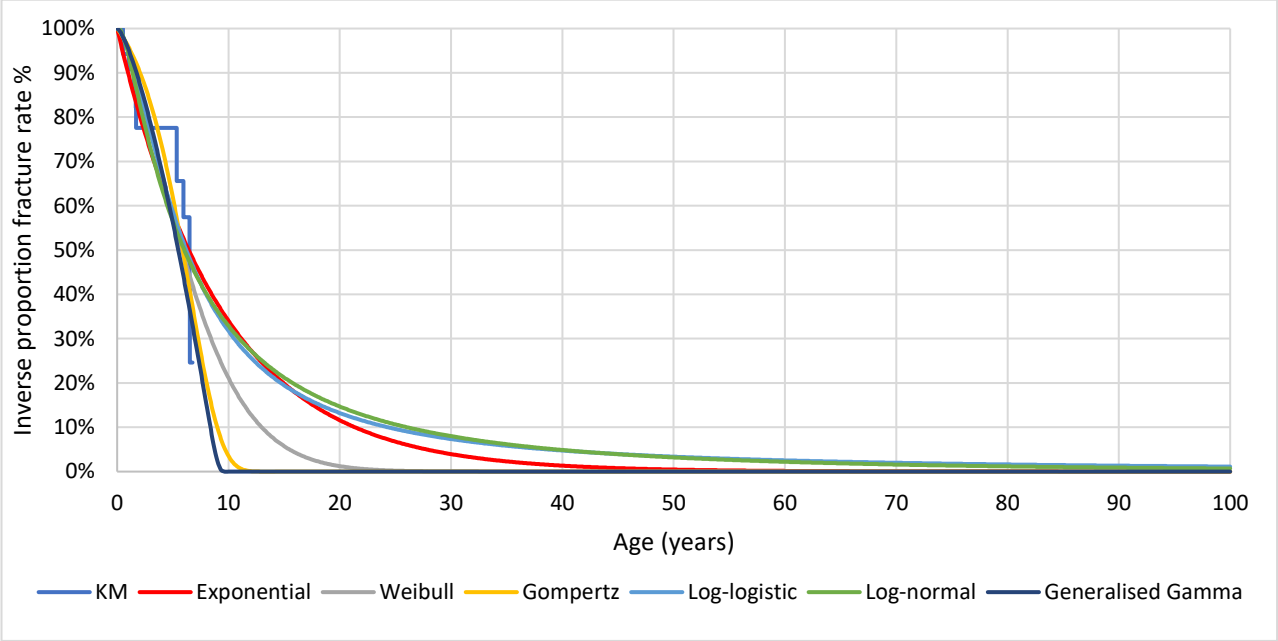
Abbreviations: KM – Kaplan Meier.
Source: Joseph et al. (2019).[5]

Figure 7: Joseph et al. (2019) – Intermittent prednisolone: all fractures long-term



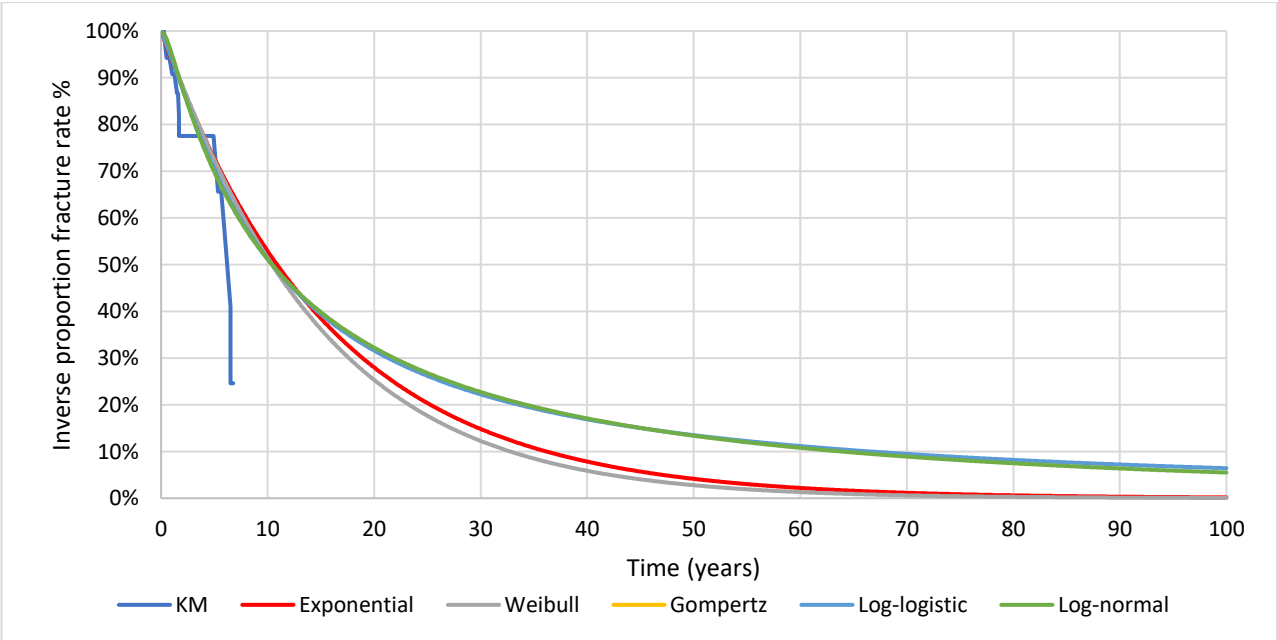
Abbreviations: KM – Kaplan Meier.
Source: Joseph et al. (2019).[5]

Figure 8: Joseph et al. (2019) – Daily deflazacort: all fractures long-term



Abbreviations: KM – Kaplan Meier.
Source: Joseph et al. (2019).[5]

Figure 9: Joseph et al. (2019) – Intermittent deflazacort: all fractures long-term



Abbreviations: KM – Kaplan Meier.
Source: Joseph et al. (2019).[5]

Table 6: Joseph et al. (2019) – Daily prednisolone: all fractures AIC/BIC goodness of fit statistics

Distribution	AIC	BIC	Sum
Exponential	201.0354	204.0527	405.0881
Weibull	199.4871	205.5216	405.0087
Gompertz	201.2586	207.2931	408.5517
Log-logistic	199.1505	205.1850	404.3355
Lognormal	199.7125	205.7471	405.4596
Generalised gamma	201.2268	210.2787	411.5055

Abbreviations: AIC – Akaike's information criterion; BIC – Bayesian information criterion; SD – Standard deviation.
Source: Joseph et al. (2019).[5]

Table 7: Joseph et al. (2019) – Intermittent prednisolone: all fractures AIC/BIC goodness of fit statistics

Distribution	AIC	BIC	Sum
Exponential	114.6421	117.5096	232.1516
Weibull	116.6042	122.3393	238.9436
Gompertz	116.5489	122.2839	238.8328
Log-logistic	116.3224	122.0575	238.3799
Lognormal	114.6058	120.3408	234.9466
Generalised gamma	107.5118	116.1144	223.6261

Abbreviations: AIC – Akaike's information criterion; BIC – Bayesian information criterion; SD – Standard deviation.
Source: Joseph et al. (2019).[5]

Table 8: Joseph et al. (2019) – Daily deflazacort: all fractures AIC/BIC goodness of fit statistics

Distribution	AIC	BIC	Sum
Exponential	85.9203	87.6092	173.5295
Weibull	85.0643	88.4421	173.5064
Gompertz	82.0909	85.4686	167.5595
Log-logistic	87.1331	90.5109	177.6440
Lognormal	87.3956	90.7733	178.1689
Generalised gamma	83.9398	89.0065	172.9463

Abbreviations: AIC – Akaike's information criterion; BIC – Bayesian information criterion; SD – Standard deviation.
Source: Joseph et al. (2019).[5]

Table 9: Joseph et al. (2019) – Intermittent deflazacort: all fractures AIC/BIC goodness of fit statistics

Distribution	AIC	BIC	Sum
Exponential	17.0167	87.6092	104.6259
Weibull	19.0104	88.4421	107.4525
Gompertz	18.5715	85.4686	104.0401
Log-logistic	18.7677	90.5109	109.2786
Lognormal	18.2770	90.7733	109.0504
Generalised gamma	16.3790	89.0065	105.3855

Abbreviations: AIC – Akaike's information criterion; BIC – Bayesian information criterion; SD – Standard deviation.
Source: Joseph et al. (2019).[5]

Figure 10: Fracture Hazard Ratios for vamorolone from CINRG and safety pool

Abbreviations: CINRG – Cooperative International Neuromuscular Research Group; SP - Safety pool.
Source: CINRG – Santhera data on file (2024).[6]

Table 11: Fracture Hazard Ratios from CINRG and safety pool

Unadjusted Hazard Ratios			
	Hazard Ratio	**Lower**	**Upper**
Deflazacort, Daily vs Vamorolone	[redacted]	[redacted]	[redacted]
Prednisone, Daily vs Vamorolone	[redacted]	[redacted]	[redacted]

Abbreviations: CINRG – Cooperative International Neuromuscular Research Group.
Source: CINRG – Santhera data on file (2024).[6]

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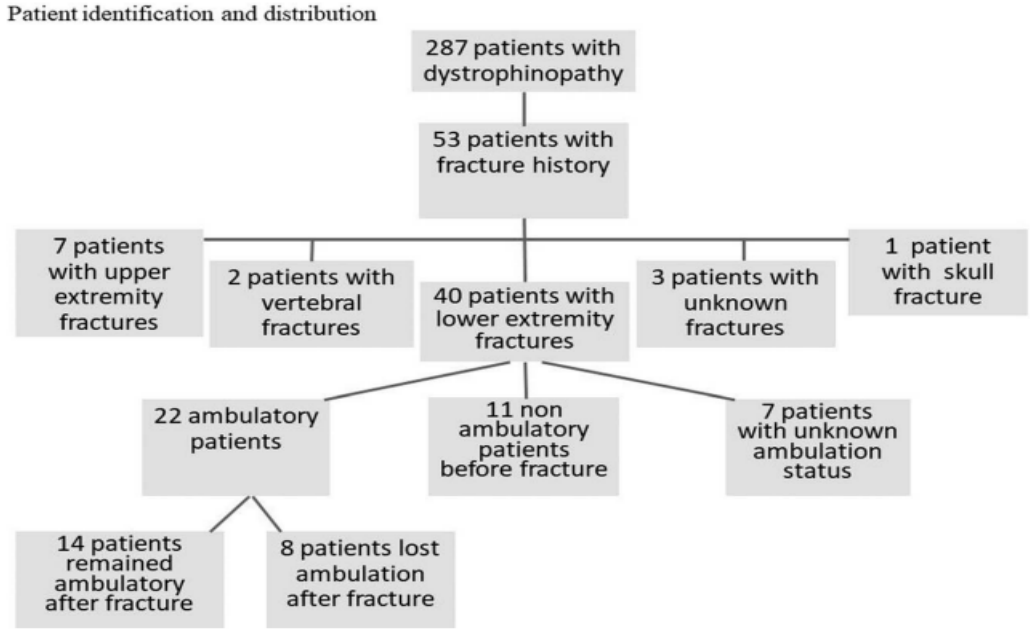
Figure 12: Vamorolone fractures probability, using CINRG HR applied to Joseph et al. prednisolone

Abbreviations: CINRG – Cooperative International Neuromuscular Research Group; HR – Hazard ratio.
Source: CINRG – Santhera data on file (2024)[6]; Joseph et al. (2019).[5]

Figure 13: Vamorolone fractures probability, using CINRG HR applied to Joseph et al. Deflazacort

Abbreviations: CINRG – Cooperative International Neuromuscular Research Group; HR – hazard ratio.
Source: CINRG – Santhera data on file (2024)[6]; Joseph et al. (2019).[5]

Figure 14: Yildiz et al. (2020) – 36.4% of patients lost ambulation following lower extremity fracture



Note: Of the 22 ambulatory patients, 8 lost ambulation after fracture.
Source: Yildiz et al. (2020).[7]

Adverse events – cataracts

Figure 15: Cataract incidence – prednisone daily CINRG (short-term)

Abbreviations: CINRG – Cooperative International Neuromuscular Research Group; KM – Kaplan Meier.
Source: CINRG – Santhera data on file (2024).[6]

Figure 16: Cataract incidence – deflazacort daily CINRG (short-term)

Abbreviations: CINRG – Cooperative International Neuromuscular Research Group; KM – Kaplan Meier.
Source: CINRG – Santhera data on file (2024).[6]

Figure 17: Cataract incidence – prednisone daily CINRG (long-term)

Abbreviations: CINRG – Cooperative International Neuromuscular Research Group; KM – Kaplan Meier.
Source: CINRG – Santhera data on file (2024).[6]

Figure 18: Cataract incidence – deflazacort daily CINRG (long-term)

Abbreviations: CINRG – Cooperative International Neuromuscular Research Group; KM – Kaplan Meier.
Source: CINRG – Santhera data on file (2024).[6]

Table 19: Cataract incidence – prednisone daily CINRG AIC/BIC goodness of fit statistics

Distribution	AIC	BIC	Sum
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]

Abbreviations: AIC – Akaike's information criterion; BIC – Bayesian information criterion; CINRG – Cooperative International Neuromuscular Research Group; SD – Standard deviation.
Source: CINRG – Santhera data on file (2024).[6]

Table 20: Cataract incidence – deflazacort daily CINRG AIC/BIC goodness of fit statistics

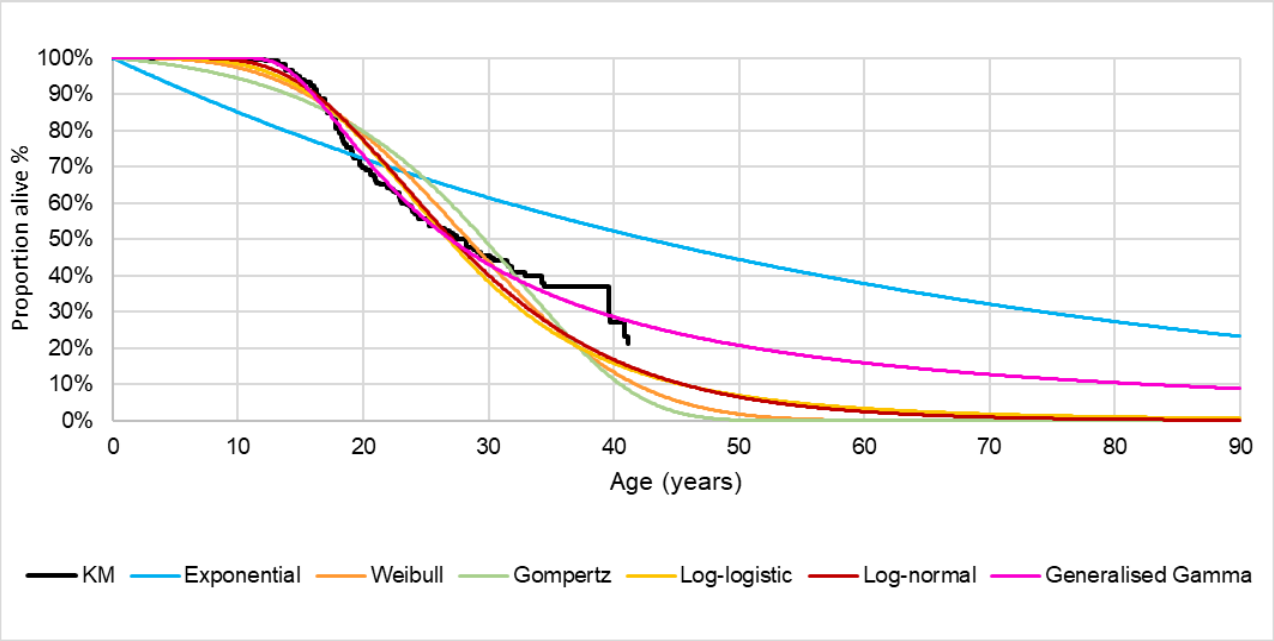
Distribution	AIC	BIC	Sum
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]

Abbreviations: AIC – Akaike's information criterion; BIC – Bayesian information criterion; CINRG – Cooperative International Neuromuscular Research Group; SD – Standard deviation.

Source: CINRG – Santhera data on file (2024).[6]

Mortality

Figure 21: Broomfield et al. (2021) – post-1990 mortality data and extrapolations



Abbreviations: KM – Kaplan Meier.
Source: Broomfield et al. (2021).[8]

Table 22: Broomfield et al. (2021) – post-1990 mortality data and extrapolations - AIC/BIC goodness of fit statistics

Distribution	AIC	BIC
Exponential	2613.851	2618.7
Weibull	2235.641	2245.339
Gompertz	2337.283	2346.981
Log-logistic	2188.159	2197.857
Lognormal	2160.478	2170.176
Generalised gamma	2110.633	2125.18

Abbreviations: AIC – Akaike's information criterion; BIC – Bayesian information criterion; SD – Standard deviation.
Source: Broomfield et al. (2021).[8]

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

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Health state utilities

Figure 23: Landfeldt et al. (2023) – DMD patient utility values associated with health states used in the base-case economic model

Health states	Utilities - EQ-5D-3L
1 - Early ambulatory	0.65
2 - Late ambulatory	0.49
3 - Transfer	0.49
4 - HTMF, no ventilation	0.31
5 - No HTMF, no ventilation	0.31
6 - HTMF, night-time ventilation	0.26
7 - No HTMF, night-time ventilation	0.26
8 - Full time ventilation	0.26

Note: Where utilities were not available for all health states, assumptions were made.
Abbreviations: DMD – Duchenne muscular dystrophy; EQ-5D-3L – EuroQoL five dimensions-3-level; HTMF – Hand-to-mouth function.
Source: Landfeldt et al. (2023).[9]

Table 24: Number of caregivers per patient per health state

Health states	Number of carers
1 - Early ambulatory	1
2 - Late ambulatory	1
3 - Transfer	1
4 - HTMF, no ventilation	2
5 - No HTMF, no ventilation	2
6 - HTMF, night-time ventilation	2
7 - No HTMF, night-time ventilation	2
8 - Full time ventilation	2

Abbreviations: HTMF – Hand-to-mouth function.
Source: Clinical validation.[10]

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Adverse events disutilities

Table 25: Moderate to severe adverse events disutilities and duration by line of treatment

		Vamorolone		Corticosteroids		No Treatment		
Adverse events	**Disutility**	**Duration of event (days)**	**QALY loss per event**	**Duration of event (days)**	**QALY loss per event**	**Duration of event (days)**	**QALY loss per event**	**Assumption**
Spinal vertebral fractures	0.065	720.00	-0.13	720.00	-0.13	720.00	-0.13	Dipnall et al. (2021).[11]
Non vertebral fractures	0.050	720.00	-0.10	720.00	-0.10	720.00	-0.10	
Weight gain	0.050	126.00	-0.02	126.00	-0.02	126.00	-0.02	A US ICER submission for DMD assumed a 0.05 disutility for a year and is applied according to the average duration of the adverse event in the specific arm for VISION-DMD.[1]
Behavioural issues	0.120	547.50	-0.18	547.50	-0.18	547.50	-0.18	Disutility calculated from de Kinderen et al. (2016)[12] for behaviour issues, specifically for irritability and aggression in a paediatric population for epilepsy.
Cushingoid effects	0.056	29.00	0.00	106.00	-0.02	29.00	0.00	A disutility for impaired physical appearance has been applied from the NICE submission HST14[13], this has been applied for the duration of average cushingoid adverse event in VISION-DMD.
Immune supressed/ infection	0.142	4.00	0.00	7.50	0.00	8.00	0.00	URTI was the most common infection which has been assumed to represent this event, as noted in Sullivan et al. (2011)[14] applied according to the average duration of the URTI in the specific arm for VISION-DMD.
GI symptoms	0.020	365.00	-0.02	365.00	-0.02	365.00	-0.02	Disutility for IBS from A study of Chronic conditions in Denmark. Hvidberg et al. (2023).[15] Assumed to last a year as a long-term event.
Diabetes	0.030	365.00	-0.03	365.00	-0.03	365.00	-0.03	Type 2 Diabetes assumed to last a year as a long-term event, from a study of Chronic conditions in Denmark Hvidberg et al. (2023).[15]

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		Vamorolone		Corticosteroids		No Treatment		
Adverse events	**Disutility**	**Duration of event (days)**	**QALY loss per event**	**Duration of event (days)**	**QALY loss per event**	**Duration of event (days)**	**QALY loss per event**	**Assumption**
Skin/Hair change	0.056	365.00	-0.06	365.00	-0.06	365.00	-0.06	A disutility for impaired physical appearance has been applied from the NICE submission HST14[13] to capture hirsutism arising as part of skin and hair changes, applied to last 1 year.
Stunted Growth	0.056	2920.00	-0.45	2920.00	-0.45	2920.00	-0.45	A disutility for impaired physical appearance has been applied from the NICE submission HST14[13] to capture the impact of short stature. This was assumed to last 8 years in line with clinical validation.
Cataracts	0.140	30.42	-0.01	30.42	-0.01	30.42	-0.01	NICE HST11[16], a disutility applied for 1-month, based on cataracts as an AE for voretigene neparvovec for treating inherited retinal dystrophies.

Abbreviations: AE – Adverse event; AESI – Adverse event of special interest; DMD – Duchenne muscular dystrophy; GI – Gastrointestinal; GP - General practitioner; HST – Highly specialised technology; IBS – Irritable bowel syndrome; ICER – Incremental cost-effectiveness ratio; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; QALY – Quality adjusted life year; UK – United Kingdom; URTI - Upper respiratory tract infection.
Sources: Dipnall et al. (2021)[11]; VISION-DMD[17]; De Kinderen et al. (2016)[12], NICE submission HST14[13]; Sullivan et al. (2011)[14]; Hvidberg et al. (2023)[15]; NICE HST11.[16]

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Table 26: Mild adverse events disutilities and duration by line of treatment

		Vamorolone		Corticosteroids		No Treatment		Assumption
Adverse events	**Disutility**	**Duration of event (days)**	**QALY loss per event**	**Duration of event (days)**	**QALY loss per event**	**Duration of event (days)**	**QALY loss per event**	
Weight gain	0.013	126.00	0.00	126.00	0.00	126.00	0.00	Assumed 50% of moderate/severe disutilities
Behavioural issues	0.030	547.50	-0.04	547.50	-0.04	547.50	-0.04	
Cushingoid effects	0.014	29.00	0.00	106.00	0.00	29.00	0.00	
Immune supressed/ infection	0.036	4.00	0.00	7.50	0.00	8.00	0.00	
GI symptoms	0.005	365.00	0.00	365.00	0.00	365.00	0.00	
Diabetes	0.006	365.00	-0.01	365.00	-0.01	365.00	-0.01	
Skin/Hair change	0.014	365.00	-0.01	365.00	-0.01	365.00	-0.01	

Abbreviations: AE – Adverse event; DMD – Duchenne muscular dystrophy; GI – Gastrointestinal; QALY – Quality adjusted life year.

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Costs

Table 27: Direct medical health states costs as reported in Landfeldt et al, 2017, inflated to 2022 price year, used in the base-case

	Early ambulatory	Late ambulatory	Transfer	HTMF, no ventilator	No HTMF, no ventilator	HTMF, night ventilator	No HTMF, night vent	Full time ventilation
Direct health care costs	£12,623	£13,238	£19,508	£19,508	£32,639	£37,513	£37,513	£43,050

Note: Direct health care costs include hospital admissions, emergency care, respite care, visits to physicians and other healthcare practitioners (i.e. nurses, general practitioners, specialist physicians, psychologists, therapists, physiotherapists, occupational therapists, care coordinators/care advisors, dentists, dietitians/nutritionists and speech/language/swallowing therapists), tests and assessments, medications, medical aids, devices and investments.
Abbreviations: HTMF – Hand-to-mouth function.
Source: Landfeldt et al 2017

Table 28: Resource use and unit cost associated with growth stunting

Activity	Currency code	Description	Unit cost
Consultant led, Endocrinology Service, outpatient care	WF01A	Non-Admitted Face-to-Face Attendance, Follow-up	£220.74
	WF01B	Non-Admitted Face-to-Face Attendance, First	£304.12

Note: 1 first attendance and 1 second attendance appointment to see a consultant endocrinologist is assumed based on clinical validation, applied per event of moderate to severe growth stunting. This replaces the growth hormone costs that were previously used in the model.
Source: NHS reference costs 2021/2022,[19] Clinical validation.[10]

Table 29: Joseph et al (2019) – Proportion of DMD patients who receive bisphosphonate treatment following vertebral and non-vertebral fractures

GC regimen	Bisphosphonate Therapy Over the Observation Period	No./Total No. (%)	Type of fractures	Incidence per 10,000 Person-Years (95% CI)
Daily deflazacort	Oral and IV	26/41 (63)	VF and non-VF	1367 (796-2188)
	Oral	18/26 (69)	VF	322 (88-823)
	IV	8/26 (31)	Non-VF	1045 (556-1787)
Intermittent deflazacort	Oral and IV	2/13 (15)	VF and non-VF	577 (119-1686)
	Oral	2/2 (100)	VF	192 (5-1072)
	IV	0	Non-VF	385 (47-1389)
Daily prednisolone	Oral and IV	3/152 (20)	VF and non-VF	748 (550-995)
	Oral	21/31 (68)	VF	223 (122-374)
	IV	10/31 (32)	Non-VF	525 (362-738)
Intermittent prednisolone	Oral and IV	13/131 (16)	VF and non-VF	512 (32-776)
	Oral	7/13 (54)	VF	186 (80-367)
	IV	6/13 (46)	Non-VF	326 (178-547)
Mixed regimen	Oral and IV	40/183 (22)	VF and non-VF	669 (516-852)
	Oral	28/40 (70)	VF	226 (142-343)
	IV	12/40 (30)	Non-VF	442 (320-596)
GC naïve	Oral and IV	0	VF and non-VF	254 (30-887)
	Oral	0	VF	0
	IV	0	Non-VF	254 (30-887)

Abbreviations: CI – Confidence interval; DMD – Duchenne muscular dystrophy; GC – Glucocorticoid; IV – Intravenous; VF – Vertebral fracture.
Source: Joseph et al. (2019).[5]

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Consultation on the appraisal consultation document – deadline for comments 5:00pm on Wednesday 24th April 2024. Please submit via NICE Docs.

Table 30: Proportion receiving bisphosphonates for treatment and vertebral type

	Daily deflazacort	Daily Prednisone	Vamorolone	No treatment
Proportion receiving any bisphosphonates by treatment	63%	20%	20%	20%
Proportion receiving oral (VF)	69%	68%	68%	68%
Proportion receiving IV (non-VF)	31%	32%	32%	32%

Note: Vamorolone and no treatment have been aligned with daily prednisone. Based on Joseph et al. 2019, IV bisphosphonates costs are only applied to non-VF and oral bisphosphonates are used for VF.
Abbreviations: IV – Intravenous; VF – Vertebral fracture.
Source: Joseph et al. (2019).[5]

Table 31: Oral bisphosphonate – average dose and cost

	Input	Assumption
Average dose (in years)	2.75	Average taken from Hawker et al (2005)[20], Houston et al (2014)[21] Srinivasan et al. (2016)[22], Zheng et al (2020)[23]
Average dose	35 mg/week	
Average cost per treatment	£39.33 for 2.75 years	Average cost taken from BNF prices[24,25]

Note: average dose taken from sources.
Abbreviations: BNF – British National Formulary; mg – Milligram.
Source Hawker et al. (2005)[20]; Houston et al. (2014)[21]; Srinivasan et al. (2016)[22]; Zheng et al. (2020)[23]; BNF – Actonel 35 mg Teva UK Ltd.[24], Alendronic acid 70 mg A A H Pharmaceuticals Ltd.[25]

Table 32: IV bisphosphonate – dose and duration

Input		Source
Zoledronic acid dose (mg/kg)	0.05	Standard of practice has shifted from using pamidronate to using zoledronic acid exclusively (Ronsley et al. 2020[26])
Administration frequency (months)	**6**	
Average duration (months)	50.4	
Total number of administrations	8.4 (average duration/ administration frequency)	Landfeldt et al. (2024)[27]

Note: 6-month duration based on clinical validation.[10]
Abbreviations: IV – Intravenous; kg – Kilogram; mg – Milligram.
Source: Ronsley et al (2020)[26]; Landfeldt et al. (2024).[27]

Table 33: IV bisphosphonate costs

IV bisphosphonates costs		Source
Unit cost	£174	Zoledronic acid 4 microgram/100ml infusion bags BNF
Unit size (mg)	4.0	
Av dose (mg)	2.4	Average dose based on the age of 12.7 for bisphosphate start of treatment from Ronsley et al. 2020
Average dose cost	£103	
Cost for one IV administration	£1,066	NHS reference costs 2021/22. AB18Z, Regular Day Admission, Continuous Infusion of Therapeutic Substance for Pain Management

IV bisphosphonates costs		Source
Total cost per person of IV bisphosphonate treatment	£9,738	(Average dose cost + AB18Z admin cost), multiplied by number of administrations

Note: Average dose based on the at age 12.7 for bisphosphate start of treatment (Ronsley et al. 2020).[26]
Abbreviations: BNF – British National Formulary; IV – Intravenous; mg – Milligram; ml – Millilitre.
Source: Ronsley et al. (2020)[26]; BNF Zolendronic acid 4 mg/100ml Atlan Pharma Ltd.[28]

Table 34: Fracture costs by treatment arm and fracture type

	SoC (Dependent on if prednisone or deflazacort is in use)	Vamorolone	No treatment
VF	£8,988	£8,977	£8,977
Non-VF	£8,889	£7,629	£7,629

Note: cost of fractures, one DEXA scan (RD50Z NHS Reference costs 2021/2022[19]), emergency steroids for surgery and a proportion receive bisphosphonates based on source selected Joseph et al (2019)[5] or Crabtree et al. (2018)[29]. Only bisphosphonate costs differ by treatment arm. Only bisphosphonate costs differ by treatment arm.
Abbreviations: SoC – Standard of care; VF – Vertebral fracture.
Source: NHS Reference costs 2021/22.[19]

Table 35: Severe non-vertebral fracture costs

Currency code	Description	Number of Events	Average Cost
Elective			
HD39D	Pathological Fractures with CC Score 11+	58	£5,950.11
HE11A	Hip Fracture with Multiple Interventions, with CC Score 8+	0	£0.00
HE21A	Knee Fracture with Multiple Interventions	0	£0.00
HE31A	Foot Fracture with Multiple Interventions	0	£0.00
HE41A	Hand Fracture with Interventions	18	£4,446.28
HE51A	Arm Fracture with Interventions, with CC Score 6+	9	£9,077.08
HE71A	Rib or Chest Fracture, with Interventions	0	£0.00
Non elective long stay			
HD39D	Pathological Fractures with CC Score 11+	3319	£5,871.52
HE11A	Hip Fracture with Multiple Interventions, with CC Score 8+	676	£11,198.14
HE21A	Knee Fracture with Multiple Interventions	350	£10,417.55
HE31A	Foot Fracture with Multiple Interventions	244	£8,659.76
HE41A	Hand Fracture with Interventions	187	£4,109.10
HE51A	Arm Fracture with Interventions, with CC Score 6+	844	£6,484.92
HE71A	Rib or Chest Fracture, with Interventions	817	£6,593.77
Weight average cos of elective and non elective			**£6,892**

Abbreviations: CC – Complications and comorbidities.

Source: NHS reference costs 2021/2022.[19]

Table 36: Cataract costs from NHS reference costs elective inpatient (2021/22)

Currency code	Description	Number of Events	Unit cost
BZ30A	Complex, Cataract or Lens Procedures, with CC Score 2+	63	£3,553.17
BZ30B	Complex, Cataract or Lens Procedures, with CC Score 0-1	52	£3,000.82
BZ31A	Very Major, Cataract or Lens Procedures, with CC Score 2+	185	£2,798.25
BZ31B	Very Major, Cataract or Lens Procedures, with CC Score 0-1	192	£3,184.76
BZ32A	Intermediate, Cataract or Lens Procedures, with CC Score 2+	34	£5,150.00
BZ32B	Intermediate, Cataract or Lens Procedures, with CC Score 0-1	47	£3,853.57
BZ33Z	Minor, Cataract or Lens Procedures	199	£882.78
Weighted average cost			**£3,255.25**

Note: Clinical validation[10] stated that due to the complex needs of DMD patients, cataracts procedures would be 'complex' in nature and require additional resource, therefore BZ33Z code is excluded.
Abbreviations: CC – Complications and comorbidities; NHS – National Health Service
Source: NHS reference costs 2021/2022[19]; Clinical validation April 2024[10]; Broomfield et al. (2021)[8]Source: NHS reference costs 2021/2022[19]; Clinical validation April 2024[10]; Broomfield et al. (2021).[8]

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Vamorolone for treating Duchenne muscular dystrophy [ID4024]

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Revised base case results

Table 37: Base case ICER

			Incremental			
	Total costs (£)	**QALYs**	**Costs (£)**	**QALYs***	**Incremental ICER**	**Vamorolone ICER vs**
Deflazacort	[redacted]	[redacted]				[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	1.12	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	3.00	[redacted]	

*Note Incremental QALYs presented have had the severity modifier applied.
Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life year.

Table 38: PSA prednisone vs Vamorolone results

Technologies	**Total Costs (£)**	**Total QALYs**	**Incremental Costs (£)**	**Incremental QALYs**	**ICER (£)**
Prednisone	[redacted]	[redacted]	[redacted]		[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	4.45	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; PSA – Probabilistic sensitivity analysis; QALYs – Quality-adjusted life years.

Table 39: PSA deflazacort vs Vamorolone results

Technologies	**Total Costs (£)**	**Total QALYs**	**Incremental Costs (£)**	**Incremental QALYs**	**ICER (£)**
Deflazacort	[redacted]	[redacted]			
Vamorolone	[redacted]	[redacted]	[redacted]	7.13	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; PSA – Probabilistic sensitivity analysis; QALYs – Quality-adjusted life years.

Figure 40: Incremental cost-effectiveness plane – vs deflazacort

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Figure 41 Cost-effectiveness acceptability curve – vs deflazacort

Figure 42: Incremental cost-effectiveness plane – vs prednisone

Figure 43: Cost-effectiveness acceptability curve – vs prednisone

Figure 44 : Tornado diagram for prednisone versus vamorolone

Abbreviations: CPRD - Clinical Practice Research Datalink; ICER – Incremental cost-effectiveness ratio; SoC – Standard of care.

Figure 45: Tornado diagram for deflazacort versus vamorolone

Abbreviations: ICER – Incremental cost-effectiveness ratio.

Table 46: OWSA results for prednisone versus vamorolone

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Prednisone transition hazard ratios	[redacted]	[redacted]	[redacted]
Efficacy of down titrated - SoC (HR)	[redacted]	[redacted]	[redacted]
Prednisone Behavioural issues	[redacted]	[redacted]	[redacted]
Direct costs by health state (Landfeldt) - Comparator 1: 8 - Full time ventilation	[redacted]	[redacted]	[redacted]
Prednisone mortality hazard ratios	[redacted]	[redacted]	[redacted]
No treatment % pts receiving spinal surgery	[redacted]	[redacted]	[redacted]
No treatment transitions hazard ratio	[redacted]	[redacted]	[redacted]
Behavioural issues: Disutilities	[redacted]	[redacted]	[redacted]
Direct costs by health state (Landfeldt) - New treatment: 8 - Full time ventilation	[redacted]	[redacted]	[redacted]
SoC % who LOA upon fracture	[redacted]	[redacted]	[redacted]

Abbreviations: CPRD – Clinical Practice Research Datalink; HTMF – Hand-to-mouth function; ICER – Incremental cost-effectiveness ratio; OWSA – One-way sensitivity analysis; SoC – Standard of care.

Table 47: OWSA results for deflazacort versus vamorolone

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Direct costs by health state (CPRD) - Comparator 1: 8 - Full time ventilation	[redacted]	[redacted]	[redacted]
Deflazacort transition hazard ratios	[redacted]	[redacted]	[redacted]
SoC Behavioural issues : Duration of event (days)	[redacted]	[redacted]	[redacted]
Vamorolone transition hazard ratios	[redacted]	[redacted]	[redacted]

Stunted Growth: Disutilities	[redacted]	[redacted]	[redacted]
SoC Stunted Growth: Duration of event (days)	[redacted]	[redacted]	[redacted]
Efficacy of down titrated - SoC (HR)	[redacted]	[redacted]	[redacted]
Behavioural issues: Disutilities	[redacted]	[redacted]	[redacted]
Behavioural issues (caregiver): Duration of event (days)	[redacted]	[redacted]	[redacted]
Direct costs by health state (CPRD) - New treatment: 2 - Late ambulatory	[redacted]	[redacted]	[redacted]

Abbreviations: CPRD - Clinical Practice Research Datalink; HTMF – Hand-to-mouth function; ICER – Incremental cost-effectiveness ratio; OWSA – One-way sensitivity analysis; SoC – Standard of care.

Table 48: Scenario analysis results

Scenario	Prednisone ICER	Deflazacort ICER
Vamorolone reduced efficacy relative to prednisone and deflazacort – 5%	[redacted]	[redacted]
Vamorolone reduced efficacy relative to prednisone and deflazacort – 10%	[redacted]	[redacted]
Vamorolone 4mg down titrated patients have 7% reduced efficacy	[redacted]	[redacted]
Landfelt 2017 health state cost	[redacted]	[redacted]
Landfeldt 2017 health state utilities	[redacted]	[redacted]
Discontinuation source for deflazacort set to prednisone	[redacted]	[redacted]
Carer behavioural disutility applied for 12 months (midpoint from clinical expert opinion	[redacted]	[redacted]
Use of bisphosphonates – assuming 100% use IV (applied to Joseph 2019)	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; IV – Intravenous; mg – Milligram.

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Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 24 April 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Muscular Dystrophy UK Action Duchenne

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None received by either charity
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to disclose by either charity
Name of commentator person completing form:	[redacted] (Muscular Dystrophy UK) [redacted] (Action Duchenne)

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Of the areas of uncertainty highlighted in the draft guidance, the experience and impact of the side effects of currently used corticosteroids was the one we identified as where further input from the Duchenne community, beyond that which we have already made, could add most value and provide most assistance to the appraisal. Muscular Dystrophy

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<table>
<tr><td></td><td>UK therefore conducted a survey vis Survey Monkey of the Duchenne community between 15 April 2024 and 21 April 2024. Action Duchenne assisted in publicising the survey and had no involvement in its design or analysis.

76 people took part in the survey. 7 respondents (9.2%) have Duchenne muscular dystrophy; 61 respondents (80.3%) are a parent of a child with Duchenne muscular dystrophy; 6 respondents (7.9%) are a carer for someone with Duchenne muscular dystrophy (we provided the NICE definition of carer); and 2 respondents (2.6%) stated “other (e.g. wider family member or friend)” and when asked for further information stated that they were a parent and a grandparent.

70 respondents stated that they or the person they care for have experience of receiving corticosteroid treatment. Those that didn’t spoke from a perspective of someone approaching their use or who had decided not to use them.

This response presents the finding of the survey and includes a selection of quotes from open text responses.</td></tr>
<tr><td>2</td><td>Severity of side effects of corticosteroid treatment
Respondents were asked how severe the impact of a range of side effects of corticosteroid treatment was on them or the person they care for on a scale of 1-5, with 1=none (no side effects); 2=minimal severity; 3=some severity; 4=moderate severity; 5=high severity.

<table>
<tr><th>Side effect</th><th>n[1]=</th><th>Mean rating</th></tr>
<tr><td>Stunted growth</td><td>68</td><td>4.1</td></tr>
<tr><td>Delayed puberty</td><td>68</td><td>3.8</td></tr>
<tr><td>Risk of fractures</td><td>67</td><td>3.7</td></tr>
<tr><td>Behavioural/emotional changes</td><td>71</td><td>3.6</td></tr>
<tr><td>Weight Gain</td><td>69</td><td>3.6</td></tr>
<tr><td>Osteoperosis</td><td>68</td><td>3.6</td></tr>
<tr><td>Issues with sleep</td><td>71</td><td>3.0</td></tr>
<tr><td>Loss of hand function</td><td>68</td><td>2.6</td></tr>
<tr><td>Cataracts</td><td>69</td><td>2.4</td></tr>
</table>

“We are currently having to weigh the benefits against the negatives. Anything that even marginally can improve his symptoms, would be a god send. Steroids are a necessary evil but alternatives if approved would be fantastic”.
“Our son is unable to tolerate the side effects of steroids and so has no treatment for his DMD. We were very much hoping that alternatives would be available this year”.
</td></tr>
</table>

[1] Number of people who provided a response to this option.

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

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<table>
<tr><td></td><td>

“The effect that weight gain has had on our son has been emotional to watch, he hates the way he looks with the weight he has gained due to the daily Corticosteroid he has to take. This has taken its toll on him both emotionally and physically”.
“The side effects have a massive effect on self-esteem. My son wants to die and some of the contributing factors are because of the side effects of steroids”.
“Undiagnosed osteoporosis led to our son becoming dependent on a wheelchair from one day to the next. The trauma for a young man is catastrophic. Also, stunted growth and delayed puberty contribute significantly to social isolation”.
“Issues connected to body shape and weight gain, anxiety, sadness and emotional fallout of weight gain and potential of bone fractures, repeated calcium infusion, mood swing all have an impact upon [name of child] and us as a family on top of the stresses and strains of living with DMD”.

</td></tr>
<tr><td>3</td><td>
Interference of side effects of corticosteroids with day-to-day activities
Respondents were then asked how much each side effect interfered with the day-to-day activities of themselves or the person they care for on a scale of 1-5, with 1=No interference; 2=minimal interference; 3 = moderate interference; 4= severe interference; and 5=unable to function.
<table>
<tr><th>Side effect</th><th>n[2]=</th><th>Mean rating</th></tr>
<tr><td>Behavioural/emotional changes</td><td>69</td><td>3.1</td></tr>
<tr><td>Risk of fractures</td><td>67</td><td>3.0</td></tr>
<tr><td>Osteoperosis</td><td>65</td><td>3.0</td></tr>
<tr><td>Weight Gain</td><td>69</td><td>2.9</td></tr>
<tr><td>Stunted growth</td><td>67</td><td>2.9</td></tr>
<tr><td>Issues with sleep</td><td>70</td><td>2.8</td></tr>
<tr><td>Delayed puberty</td><td>66</td><td>2.6</td></tr>
<tr><td>Loss of hand function</td><td>65</td><td>2.4</td></tr>
<tr><td>Cataracts</td><td>65</td><td>1.9</td></tr>
</table>
</td></tr>
<tr><td>4</td><td>
Focus on behavioural/emotional changes
Behaviour change, which was identified as the side effect with the most severe level of interference on day-to-day activities, can be hard to quantify and as presented earlier in the appraisal process and during the ACM1 discussion is one of particular concern amongst the Duchenne community. The survey therefore explored behaviour change in more detail. Survey respondents were asked about the frequency of behavioural/emotional issues. 68 people responded.
<table>
<tr><th>Frequency of behavioural issues</th><th>Number</th><th>Percentage</th></tr>
<tr><td>Not applicable</td><td>10</td><td>13.9%</td></tr>
</table>
</td></tr>
</table>

[2] Number of people who provided a response to this option.

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Draft guidance comments form

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Rarely	2	8.3%
Some of the time	12	16.7%
Often	26	36.1%
All of the time	18	25%

- *"Our son has had two short trials of steroids - Deflazacort. He already has behaviour/learning challenges. The addition of the steroids was completely unmanageable for him and us. He was so disregulated that we could not take him anywhere; he was extremely distressed most of the time; was not safe at school and could not attend to any education. He has had to stop steroid treatment".*

- *"When your child starts steroids you see a relatively immediate change in them. Our son became extremely unsettled emotionally and prone to angry outbursts and aggression, you can see his eyes go as rage takes over and then he will later often cry and become upset as if he has almost scared himself. He has had lots of problems at school and can only manage a reduced timetable at the moment due to behavioural issues".*

- *"My son is angry, he has huge meltdowns and cannot comprehend the environment around him. He is physically violent and will hurt himself and others. The boy he was before taking steroids is very different, he now screams, shouts and gets angry over minor things. It breaks my heart that my little boy is battling these horrific side effects".*

- *"My son has become very emotional, with large swings in behaviour, with more tantrums. He has long periods of becoming hyper and uncontrollable. He gets far normally irritated and frustrated".*

- *"We often feel devastated and overwhelmed from the Behavioural/Emotional changes the corticosteroid treatment has on our child. This is badly affecting our quality of life, social contacts and activities".*

4

Potential improvement in quality of life from side effect reduction

Respondents were then asked how much improvement to the quality of life of them or the person they care for would a reduction in each side effect of corticosteroid treatment have on a scale of 1-5, with 1=no improvement; 2=limited improvement; 3=some improvement; 4=moderate improvement; 5=significant improvement.

Side effect	**n[3]=**	**Mean rating**
Weight Gain	68	4.2
Stunted growth	66	4.2
Osteoperosis	68	4.2
Risk of fractures	67	4.0
Behavioural/emotional changes	69	4.0

[3] Number of people who provided a response to this option.

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Delayed puberty	67	3.9
Issues with sleep	68	3.6
Loss of hand function	66	3.5
Cataracts	65	3.1

5

Detailed experiences

At the end of the survey, respondents were asked if they would like to share anything else about their experience of coriticosteroid treatment. 36 people took this opportunity and here we share two of the most detailed.

- *"The side effects have been horrendous. We are in a horrible and devastating position of a child with a degenerative condition, the only drug option to slow down the decline currently has enormous side effects and we battle this every single day. The mental [health] of my son and myself/partner as his carers suffers greatly, there is no support for the boys and no support for parents who are dealing with these huge side effects. It puts enormous pressure on families to recognise the side effects and be confident in an emergency situation to explain these issues to professionals who often have no clue about DMD and side effects of steroids. For example, my son was recently admitted to hospital with a sickness bug and high temperature that he couldn't keep down. The doctor prescribed ibuprofen which boys on steroids cannot take, the lack of awareness in professionals about this is shocking".*

- *"The side effects of corticosteroids have a profound and in some cases devastating effect on boys with Duchenne. As parents when we are told about steroids being the only option to us the consultants then tell us all the side effects and we are asked to decide whether we want out child to do this but it is an impossible choice. We are essentially asked to choose between osteoporosis and earlier loss of ambulation, respiratory and heart failure. No one should have to make this choice for their child especially if there is an alternative. My 5-year-old son already had weak bones just simply as a result of his Duchenne and evidence shows bone density decreases by as much as 40% in the first year of taking steroids so we are now terrified what his DEXA scan and spinal X-ray will show this year. Parents agonise over the choice and some eventually choose not give their child steroids fearing the horrific side effects despite what this could mean for the progression of their Duchenne because they fear that they will be prolonging their life in some ways but destroying what quality of life they have. Duchenne itself is a brutal, devastating disease and anything we can do to alleviate our boys suffering should and must be done. The side effects of steroids necessitate many additional doctors appointments, scans, tests and treatments all adding to the stress and trauma people with Duchenne already have to go through if an alternative treatment could alleviate even a little of this burden it would have enormous value. Whenever our son complains of back pain or has a fall we find ourselves wondering if he has a vertebral or other fracture. No five-year-old should be at risk of this because their bones have been destroyed and continue to be destroyed by the medicine we as parents give them each day. Similarly watching them struggle with rage and extreme feelings and emotions they don't understand and knowing that it is related to steroids is difficult to explain and*

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	manage. They trust us to help and look after them and sometimes the guilt of knowing that what we are giving them is causing untold harm as well as good is too much to bear".
6	The Duchenne community expresses concerns regarding the cost implications of Vamorolone and its potential impact on the cost-benefit analysis. With limited treatment options available, any new therapy brings hope and anticipation. However, the affordability and accessibility of these treatments are paramount considerations for the community. There are sentiments of fear that the high cost of Vamorolone could pose significant challenges for healthcare systems, potentially limiting access for those who could benefit from it the most.
7	Parents are raising concerns about the impact of steroid side effects on the well-being of their children. They share stories of their sons who, after switching from prednisolone to deflazacort to manage Cushingoid appearance, found no relief and faced worsened side effects. They mention self-esteem problems, bullying from peers, and increased anxiety. This underscores the need for alternative treatments beyond steroids. It's crucial to note that these side effects, while common among DMD patients, often go unrecognized within current guidance. Therefore, it's vital that these concerns are acknowledged and addressed to provide comprehensive support for those affected by DMD.
8	There is concern within the Duchenne community regarding the clarity of the guidance on the efficacy of Vamorolone. Clear and comprehensive guidance on the efficacy of Vamorolone is crucial for informed decision-making and ensuring the best possible outcomes for individuals living with Duchenne muscular dystrophy.

Insert extra rows as needed

Checklist for submitting comments

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	ABN

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Guidance has not sufficiently taken into account the fact that in a proportion of patients who cannot tolerate prednisolone there is no alternative treatment and they will therefore have no treatment for their disease. Vamorolone should be

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	compared versus placebo as for those with significant behavioural side effects as there is no other alternative. In the adult DMD cohort, patients who stop all steroid therapy have earlier, greater ventilatory needs and worse cardiac outcomes (Pietrusz A et al (2023) Neuromuscular Disorders. Vol. 33, Sup 1, p.S106-S107). This needs to be taken into account when assessing vamorolone. The consultation has only considered Vamorolone as a direct competitor to prednisolone or deflazacort. It has not addressed the possibility of vamorolone as a second line agent for use in cases of failure to tolerate prednisolone which is likely to be where its greatest use and benefit lies. In these patients there is no current alternative apart from progressive decline. The evidence used under-represents the real world experience in adult DMD patients who have a much higher rate of stopping steroid treatment due to side effects.
2	Clinical and cost effectiveness should consider vamorolone vs placebo in cases of failure of steroid intolerance, rather than just vamorolone vs prednisolone or deflazacort. Steroid intolerance occurs more often in the more severe DMD patients and therefore have a higher risk of rapid decline and sudden death and a higher need for non-invasive ventilation and cardiac support. This increased and earlier care need has not been accounted for in the cost effectiveness.
3	We feel that it would be more appropriate to recommend Vamarolone as a second line following prednisolone/deflazocort failure, as this is where its greatest use lies. This has not been fully and properly considered in the decision
4	This recommendation discriminates against patients with learning disabilities, ADHD, autism and pre-existing psychiatric difficulties which make up around 1/3 of the adult DMD population. These are the patients who do not tolerate the behavioural side effects of prednisolone and are much more likely to discontinue use and therefore have a higher morbidity and earlier mortality. This cohort should be given separate consideration and we suggest specifically considering vamorolone use in this group when steroids have to be discontinued. They are also the group that are harder to complete comprehensive studies in because of their cognitive impairments which further increases their inequality of access to care (L. Nart et al Neuromusc disorders 2024; 35: 13-18).
5	VISION-DMD considers side effects to 24weeks and not long-term side effect profiles including into adulthood. The modelling performed of outcomes and adverse events is unreliable. Outcomes including 6MWT are variable and poor measures.
6	Behavioural concerns can appear later in the course of treatment and as noted in the review (3.7) and are a major concern for patients, families and clinicians. If such side effects are experienced on prednisolone, and no alternative medication option is available to patients, leading to treatment cessation and subsequent deterioration in neuromuscular and respiratory function, the impact on quality of life and economical impact on society and NHS is considerable.
6	The cost effectiveness analysis does not fully take into account the long term co-morbid impact of prednisolone such as cardiac disease, bone disease. It also does not account for the subsequent cost implications of a lack of alternative effective therapy to prednisolone in those forced to stop it because of side effects.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that the committee accepted the EAG view that the Vision DMD study demonstrated that Vamolorone was less effective than Prednisolone at stabilising muscle function and slowing decline in motor skills. There was NO significant difference in the 2 groups in the Vison study or in the 2 yr LTE study looking at outcome of Vamolorone treated patients in

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	comparison to matched patients on 'conventional' glucocorticoids: Prednisolone or deflazacort in both the CINRG (US) or Northstar (UK) natural history studies (Mah et al JAMA 2022). It seems disingenuous to decide that a non significant difference is somehow relevant in this study when it would not usually be considered as sufficient to exclude a null hypothesis in any well conducted clinical trial. In turn, extrapolating non significant differences into clinically meaningful differences for patients would not be considered good practice. The majority of patients in Vision DMD have elected to remain on treatment as they and their treating clinicians feel it is as effective as other glucocorticoids and the side effect profile is beneficial for the boys. In my case load 4/6 patients remain on Vamolorone. 1 family wanted to discontinue steroids treatment as a whole given the limited perceived benefit and excess weight gain and the other found the additional rigour of the compassionate use programme too onerous. 2 patients electing to remain on Vamolorone have been unable to take part in further clinical trials including exon skipping studies- as this would have mandated a switch to alternative steroids and the families did not want to discontinue Vamolorone.
2	As noted steroid side effects are a considerable concern and burden for those with DMD on long term treatment with Prednisolone and Deflazacort. Both drugs have a similar incidence of side effects but the profile is reportedly different between the 2 drugs, though only the FOR DMD study (Gugileri et al JAMA 2022) has compared the 2 in a head to head study and showed no difference. There is some further analysis looking at bone health in the FOR DMD study cohort as analysis of the natural history datasets suggests that Deflazacort may be associated with a higher rate of fracture and more restriction in growth than prednisolone. Therefore reducing the side effect burden whilst maintaining corticosteroid effect on disease slowing is a considerable benefit in DMD. It is moderate/severe effects that have the greatest impact on the boys and their families, and which are most likely to result in reducing dose and potential effectiveness. Therefore, I disagree with the EAG view that the impact on moderate/severe SEs which was considerably less in the Vamolorone v prednisolone group in the study should be disregarding as the overall side effect profile was similar. The LTE study and my own clinical experience indicates that growth is preserved on Vamolorone in comparison to other corticosteroids. Restricted height is a considerable worry for these boys and their families. It results in low self esteem and increases the risk of behavioural issues and school refusal. Preserving growth is an important benefit of Vamolorone and may in turn reflect less impact of the drug on bone health - an issue that is currently being studied in more detail.
3	Whilst Standards of care now recommend life long steroids, Vamolorone is likely to be most relevant to younger boys where growth preservation is important. Thus, as well as being an important treatment choice for steroid naïve patients, clinicians would want to have the option to 'switch' pre pubertal patients who have restricted growth or other moderate/severe side effects on prednisolone or deflazacort. My priority would be to have access to Vamolorone for steroid naïve patients and pre-pubertal boys experiencing significant SEs on prednisolone and deflazacort that may limit treatment dose and effectiveness. This would be particularly important in those with restricted growth. There is less clarity regarding benefits of switching in older boys/men who are post pubertal and tend to be on lower doses of conventional GCs.
4	I disagree with the EAG position that the model for 'stopping/discontinuation' of steroids should not be based on the UK northstar dataset figures of proportionate prednisolone: deflazacort use as

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	this is representative of the break down of 'real world' medication choice in the UK. Whilst there has been pressure from social media groups to use deflazacort in preference to prednisolone, this is not standard practice and there are many boys in the UK on prednisolone. Given the emerging questions about greater impact on bone health, the percentage opting for deflazacort in the 1st instance may change again in the next few years.
5	I concur with the concerns re the life expectancy model developed by Hercules which does suggest a somewhat unexpected survival rate after 30 yrs assuming present standards of care. I agree that there is more likely to be a continued fall in survival with time and far few DMD survivors in their 40s and 50s.
6	

Insert extra rows as needed

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Single Technology Appraisal

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

You can use the below comments: MHRA has medically and clinically approved of Vamorolone as an alternative steroid to Prednisone/Prednisolone and Deflazacort because of the evidence of less damage specifically to bone health and because it allows for growth. Long term steroid use of Prednisone, Prednisolone and Deflazacort causes Osteoporosis which can lead to bone fractures and early loss of ambulation. Osteoporosis itself has to be treated by Zoledronic acid infusions at NHS hospitals and additional medication is required. To not have to treat the negative side-effects of Deflazacort/Prednisone/Prednisolone would bring huge clinical, physical, economic and psychological benefits. Duchenne boys wants to grow. Keeping Duchenne boys healthier for longer is not only better for patients, but for the overall contribution to a better society in England. It will save cost in the long term to keep a DMD patient healthier for longer. please approve for the children affected & give them the opportunity of a better life.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I don't believe that it has, no consideration seems to have been given to the positive effects this could have on the mental health of the patient, their parents & wider family members. As there are known positive outcomes for this drug, the ability to access it will offer hope to the families and as the patient matures into a more mature understanding of the condition they have it will provide hope for their future.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Not really, the drug has strong evidence of benefit & has been approved for prescription in the USA, therefore there is already a case for it being beneficial (not only in terms of physical benefit, but also in terms of mental benefit)

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, there are so few options available for DMD patients & such a short timescale to make a difference, that to withhold a valid treatment just to conduct further modelling (rather than necessary safety checks) seems unnecessarily harsh.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, this disease affects predominantly young people, the majority of whom are male & also, largely, of white ethnicity. Withholding the treatment could be construed as falling under all the categories of age, gender, race & disability discrimination, as funding is effectively steered away from these groups. It seems that because they form a relatively small group they are being forgotten about & not supported.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

The current treatment has awful effects for young children, surely this preventative measure is more favourable for the children and their families. This should be revised:

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Comment on the draft guidance consultation

Clinical effectiveness

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Adverse events

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available

for those who wish to change their treatment regime as well as steroid naive patients.

Recommendations

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes

Comment on the draft guidance consultation

MHRA has already granted their medical & clinical regulatory approval to provide Vamorolone as an alternative steroid to Prednisone/Prednisolone and Deflazacort. The clinical evidence of Vamorolone is of less damage specifically to bone health and because it allows for growth. This in turn reduces the risk of bone fractures and bone breaks which can lead to earlier loss of ambulation. We appeal to NICE to provide this treatment option to Duchenne boys in England. Long term steroid use of Prednisone/Prednisolone and Deflazacort causes Osteoporosis. My son has Duchenne, he already has Osteoporosis and 3 spine fractures. He has to undergo Zoledronic acid treatment infusions at an NHS hospital and

additional medication to treat his Osteoporosis. This in turn causes more negative side-effects. This is all avoidable - to not have to treat the negative side-effects of bone infusions due to Deflazacort/Prednisone/Prednisolone side-effects. The clinical, physical, economic and psychological benefits far outweigh preventing the availability of the option of Vamorolone. Our son's Neuromuscular Consultants at NHS Evelina and NHS GOSH are keen for our son to switch to Vamorolone as soon as possible. Our son wants to grow. He wants to attend University and have a career. Keeping Duchenne boys healthier for longer is not only better for patients, but for the overall contribution to a better society in England. It will save cost in the long term to keep a DMD patient healthier for longer.

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Boys with DMD suffer huge side effects on the current steroids and as a result costs the
NHS more to manage in the long term

Comment on the draft guidance consultation

Boys with DMD suffer huge side effects on the current steroids and as a result costs the
NHS more to manage in the long term

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Comment on the draft guidance consultation

Boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more!! Please reverse your decision.

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Has all of the relevant evidence been taken into account?

No comment

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is my view that the emotional burden of the side effects posed by prednisolone and daflazacort has not been considered fully. Whilst vamolorone is dear at £4,485 per 100ml excluding VAT, the true emotional cost of a young child with a vertebral fracture and likely to suffer more cannot be truly or fairly weighed against this monetary value. With so few of these children in the UK probably bearing more disease burden than most other citizens, it is surely for these children that the NHS must exist.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Whilst I am not the most qualified person to talk about this, I am concerned that with Vamolorone having been approved in the US and the European Union, with a lot of the funding coming from Duchenne UK, Britain's leading DMD charity, it's lack of availability in the NHS is surely sending the wrong message to the different shareholders in the condition. Firstly to sufferers of the disease in saying that they cannot receive the best available treatment in this country and must therefore go abroad to be able to receive this treatment, to clinicians in that they cannot offer the most up to date and proven treatments to their patients with DMD, thereby leaving them behind and unable to be part of the most up to date conversation on the condition and parents who have spent years fundraising to support their charity's promise to fund research. In my view, it demonstrates a hopeless view of the future of the NHS for sufferers of DMD.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Unsure

Comment on the draft guidance consultation

I am a NHS Health visito and the mother to a 2-year-old diagnosed with Duchenne muscular dystrophy in 2023.

DMD is a rare but well documented devastating muscle disease which affects the child and the family in many ways both physically and mentally. When our son was diagnosed with DMD in 2023, we were absolutely crushed by the news but encouraged to hear that there was an alternative to standard corticosteroid therapy on the horizon which could alleviate a lot of the secondary burden of disease due to the side effects of these steroids. Over the course of the life of our son, as a family, we expect to undergo multiple challenges along the way. One of these challenges will be the side effects of the corticosteroids that our son will be prescribed from around the age of 4. The side effects of corticosteroid treatments available on the NHS are numerous, well documented and harmful. The main reported ones are weight gain, behavioural issues, growth restriction, reduced bone density/fractures and delayed puberty. Other common side effects include adrenal crisis, diabetes mellitus, hypertension, skin problems and increased infections.

As a practicing clinician on the NHS, I detest having to consent to my son being on these drugs for the rest of his life so seeing the evidence for the efficacy of Vamolorone at reducing the inflammation of DMD but without some of the worst side effects of corticosteroids really was welcome news.

It was therefore heart-breaking to learn that NICE have recently decided not to recommend that Vamolorone be made available for the treatment of children with Duchenne muscular dystrophy as it’s not been considered to be an efficient use of NHS resources.

As a family, we have accepted that our son’s life is going to be more difficult than most other peoples but we remain committed and determined to make sure that he has a fulfilling one with as best a quality of life as possible. With this in mind, it is quite concerning that despite the evidence in the multiple studies published and the fact that this drug has been approved in the US and the European Union, that NICE have not supported that this drug be made available to the few sufferers of DMD. There are about 2500 people living in the UK at any one time and whilst that might not be as many as some other conditions in the UK, those living with DMD surely are some of the most in need of any new treatments which can alleviate their disease but without the added burden of egregious adverse effects.

Whilst I am not qualified to make recommendations for what the NHS should spend its money on, I would wish that you consider the extra burden posed by these side effects of the standard Prednisolone or Deflazacort treatment on the short lives of these children and the family members that love and care for them. Vamolorone amongst other reported effects has

been shown in multiple studies to help their disease whilst sparing their growth and with reduced risk of fractures, reduced behavioural concerns and with less weight gain and the associated issues within that.

I ask that you please reconsider your decision.

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Has all of the relevant evidence been taken into account?

No.
Boys with DMD suffer huge side effects on the current steroids including; weight gain, brittle bones, delayed growth, lowered immunity, mood changes... So on. It means long term, boys usually spend a lot of time in hospital, receiving care and as a result costing the NHS more to manage in the long term. The side effects of the new drug DO NOT include stunted growth, weight gain or brittle bones.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.
Boys with DMD suffer huge side effects on the current steroids including; weight gain, brittle bones, delayed growth, lowered immunity, mood changes... So on. It means long term, boys usually spend a lot of time in hospital, receiving care and as a result costing the NHS more to manage in the long term. The side effects of the new drug DO NOT include stunted growth, weight gain or brittle bones.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No.
Boys with DMD suffer huge side effects on the current steroids including; weight gain, brittle bones, delayed growth, lowered immunity, mood changes... So on. It means long term, boys usually spend a lot of time in hospital, receiving care and as a result costing the NHS more to manage in the long term. The side effects of the new drug DO NOT include stunted growth, weight gain or brittle bones.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes.

Boys with DMD suffer huge side effects on the current steroids including; weight gain, brittle bones, delayed growth, lowered immunity, mood changes... So on. It means long term, boys usually spend a lot of time in hospital, receiving care and as a result costing the NHS more to manage in the long term. The side effects of the new drug DO NOT include stunted growth, weight gain or brittle bones.

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Has all of the relevant evidence been taken into account?

No

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Comment on the draft guidance consultation

Highly disagree with this decision

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Comment on the draft guidance consultation

Comment 1 - Clinical effectiveness

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment 2 - Adverse events

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Comment 3 - Recommensation

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an

effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

It seems that way

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is my view that the emotional burden of the side effects posed by prednisolone and daflazacort has not been considered fully. Whilst

vamolorone is dear at £4,485 per 100ml excluding VAT, the true emotional cost of a young child with a vertebral fracture and likely to suffer more cannot be truly or fairly weighed against this monetary value. With so few of these children in the UK probably bearing more disease burden than most other citizens, it is surely for these children that the NHS must exist.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not feel suitably qualified to answer this question however I am concerned that with Vamolorone having been approved in the US and the European Union, with a lot of the funding coming from Duchenne UK, Britain's leading DMD charity, it's lack of availability in the NHS is surely sending the wrong message to the different shareholders in the condition. Firstly to sufferers of the disease in saying that they cannot receive the best available treatment in this country, to clinicians in that they cannot offer the most up to date and proven treatments to their patients with DMD and parents who have spent years fundraising to support their charity's promise to fund research. In my view, it demonstrates a hopeless view of our NHS.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am unable to comment.

Comment on the draft guidance consultation

I am an NHS GP and the father to a 2-year-old diagnosed with Duchenne muscular dystrophy just a few days before his second birthday in 2023. It has taken me several days to read the draft guidance and I wished to make a comment with some of my feelings on the issue.

DMD is a rare but well documented devastating muscle disease which affects the child and the family in many ways both physically and mentally. When our son was diagnosed with DMD in 2023, we were absolutely crushed by the news but encouraged to hear that there was an alternative to standard corticosteroid therapy on the horizon which could alleviate a lot of the secondary burden of disease due to the side effects of these steroids. Over the course of the life of our son, as a family, we expect to undergo multiple challenges along the way. One of these challenges will be the side effects of the corticosteroids that our son will be prescribed from around the age of 4. The side effects of corticosteroid treatments available on the NHS are numerous, well documented and harmful. The main reported ones are weight gain, behavioural issues, growth restriction, reduced bone density/fractures and delayed puberty. Other common side effects include adrenal crisis, diabetes mellitus, hypertension, skin problems and increased infections.

As a practicing doctor on the NHS, I am loath to have to consent to my son being on these drugs for the rest of his life so seeing the evidence for the efficacy of Vamolorone at reducing the inflammation of DMD but without some of the most common and egregious side effects of corticosteroids really was welcome news.

It was therefore heart-breaking to learn that NICE have recently decided not to recommend that Vamolorone be made available for the treatment of children with Duchenne muscular dystrophy as it's not been considered to be an efficient use of NHS resources.

As a family, we have accepted that our son's life is going to be more difficult than most other peoples but we remain committed and determined to make sure that he has a fulfilling one with as best a quality of life as possible. With this in mind, it is quite concerning that despite the evidence in the multiple studies published and the fact that this drug has been approved in the US and the European Union, that NICE have not supported that this drug be made available to the few sufferers of DMD. There are about 2500 people living in the UK at any one time and whilst that might not be as many as some other conditions in the UK, those living with DMD surely are some of the most in need of any new treatments which can alleviate their disease but without the added burden of egregious adverse effects.

Whilst I am not qualified to make recommendations for what the NHS should spend its money on, I would wish that you consider the extra burden posed by these side effects of the standard Prednisolone or Deflazacort treatment on the short lives of these children and the family members that love and care for them. Vamolorone amongst other reported effects has been shown in multiple studies to help their disease whilst sparing their growth and with reduced risk of fractures, reduced behavioural concerns and with less weight gain and the associated issues within that.

We urge that you please reconsider your decision.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. Boys with Duchenne do not have time to waste. The evidence shows that Vamorolone has less side effects that current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment options.

Comment on section 3.4 (Committee discussion, Clinical effectiveness)

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamorolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment on section 3.23 (Committee discussion, Recommendation)

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Comment on section 3.15 (Committee discussion)

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

Boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. The report has not considered the mental health impact on the patient and their circle. An improvement in side effects and day to day life can have a significant impact on the patient and their circle. Anything that improves the day to day life of children should be given the opportunity to do so.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. The report states that the drug is not cost effective however the report also clearly states it can be beneficial for patients. Any benefit to children should be regarded as a good investment and cost effectiveness, especially considering the cost to the NHS in the long term with current severe side effects.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The report acknowledges that there is a high need for alternative treatments for DMD. Whilst the drug may not be recommended as the primary treatment option, providing as an option to healthcare providers and patients through the NHS should be authorised given the acknowledged benefit this treatment can deliver. Children should have the opportunity to access a treatment which improves their life experience, albeit within the challenges of living with DMD.

It isn't fair to make this decision based on a cost effectiveness calculation that is used for other treatments which don't have the same level of impact on the patient. It is important for healthcare as a whole and patients that treatments are providing as an option based on more than cost. Improved treatments improves lives and provides hope.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No. This is a disease that primarily impacts on children.

Comment on the draft guidance consultation

The current treatment for DMD leads to significant side effects for patients. The proposed new treatment reduces these side effects therefore reducing the impact on the NHS (cost, time, resource) and delivering a positive impact on the patients (children suffering with DMD).

DMD is a condition that has a huge mental health impact on the patient (having an impact on their life at such a young age and coming to terms with their future) and their family and friends who are supporting the patient and processing the impact of the condition on their loved one.

Treatments for DMD are few and far between. Because the condition has such a huge impact on a vulnerable age group (and their circle), any available treatment should be seriously considered and rolled out providing there are no serious impacts of this (the drug is currently being prescribed and is seen as safe).

Cost effectiveness isn't a suitable reason to turn this down, and is cruel, when it can significantly improve the side effects and day-to-day of children and the mental health of their circle.

However, if we must consider cost then making a treatment available which reduces potential side effects and therefore costs to the NHS should be seen as a significant positive.

Giving medical teams, care givers and parents the opportunity to make this decision for their patients and loved ones is the right thing to do and should be the foundation principle of healthcare.

Comment on section 1.2 (Recommendations) text “This recommendation is not intended to affect treatment with vamorolone that was started in the NHS before this guidance was published.”

If Vamorolone has been used prior to this guidance then families should still be given the opportunity to access this. Cost effectiveness isn't a sufficient argument when treatment can impact the lives of children and when the current steroid side effects can cost the NHS more in the long term.

Comment on section 1.2 (Recommendations) text "Because of the uncertainties in the clinical evidence and economic model, it is not possible to determine the most likely cost-effectiveness estimates for vamorolone. So, further modelling is needed, and vamorolone is not recommended."

I support the proposal for further modelling however this treatment should still be made available to medical professionals and patients in the meantime. Children are suffering from side effects that could be improved with the new treatment. They should be given the hope and opportunity to improve their day to day life. Further modelling can help to judge whether this should be the recommended course of treatment but in the meantime families should be able to make this decision.

Comment on section 3.3 (Committee discussion, Treatment options), text "The committee concluded there is a need for effective treatments for DMD with less side effects than standard corticosteroids."

Given this need, surely it is important to offer patients the chance to try a treatment which would deliver less severe side effects. Side effects often lead to medical intervention which will cost the NHS more to address in the long term than funding the availability of vamorolone.

Comment on section 3.4 (Committee discussion, Vamorolone positioning), text "The clinical and patient experts also noted that there would likely be some people having current treatments that would want to switch to vamorolone for its anticipated better safety profile."

Given the experts have acknowledged that some patients would want to switch for its anticipated better safety profile, how can we justify not offering these people the chance to do so when a potentially better treatment is available. Further modelling can still continue. DMD patients who are so young deserve the opportunity to improve their day-to-day life. It could also reduce the impact on their network.

Comment on section 3.24 (Committee discussion, Recommendation), text "The committee concluded that there was not enough evidence to conclude that vamorolone is a cost-effective treatment option. So, it did not recommend vamorolone for treating DMD in people 4 years and over."

The committee agreed that vamorolone is an effective treatment but it isn't being recommended due to cost-effective reasoning. Given the cost to the

NHS in dealing with the side effects and impact on their network, I ask that the committee reconsider their decision. I understand that resources are finite however when a safe and effective treatment becomes available for a disease that the report states has a high unmet need, severe impact on patients (children) and severe side effects (which have a significant impact on the patients and NHS resources) should be made available as a choice. There are not a lot of other treatment possibilities with DMD and patients and carers need all the support they can get to manage this condition as best as they can. Making it possible to reduce side effects for children is the humane decision.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

When there is a treatment that is already developed that can give Duchenne boys hope and a chance of treatment without the side effects of Steroids, the UK has a duty and a responsibility to make that treatment available.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

Boys with DMD suffer huge side affects from the current steroids and as a result costs the NHS more to manage in the long term.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Boys suffer tremendous side effects with the steroids that are currently offered, which in fact costs the NHS more money in the long term.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Boys suffer tremendous side effects with the steroids that are currently offered, which in fact costs the NHS more money in the long term.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Boys suffer tremendous side effects with the steroids that are currently offered, which in fact costs the NHS more money in the long term.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Boys suffer tremendous side effects with the steroids that are currently offered, which in fact costs the NHS more money in the long term.

Comment on the draft guidance consultation

Boys with DMD suffer tremendous side effects with the current steroids offered, which in the long term actually costs the NHS more money.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

Boys with DMD suffer huge side effects on the current steroids and as a result cost the nhs more to manage in the long run

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No, I do not believe it has.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, I do not believe they are.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not agree with the content in full.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Comment on section 3.2 (Committee discussion, Impact of the condition)

Please do not underestimate the impact of this rare condition and the effects it is having on our 7-year old son, his family and friends. To see your apparently healthy baby gradually grow weaker, to not be able to grow, develop and explore as his peers is soul destroying. When we received the devastating news that our son has DMD our world fell apart. To be told there is no cure is just as devastating. To then be told that the only treatment to try and prolong ambulation and his life is high-dose steroid treatment tears you apart.

You are not directed to place your child on steroids but given the option. The reason being - the long and crippling side-effects of the drug. A child's growth is stunted, his bones grow weaker and will break, his behaviour will be negatively impacted, his face will become distorted, he will put on weight, his eyesight will likely deteriorate, he will be at high risk of adrenal crisis. The list goes on. We eventually chose to place [redacted] on Prednisolone. That decision is a very hard one to have to live with. Every day our son willingly takes this medicine. Every time he takes it we feel pain and guilt. The very treatment he's taking is causing so much damage itself. We do not sleep well, our mental health, work and home-life have suffered. Sometimes the stress becomes unbearable and we find it extremely difficult to cope.

To have access to a medication that significantly reduces some of those side effects is essential. Vamorolone is a dissociative steroid with significantly reduced side effects - particularly bone health and growth. The most important concern for us is bone health. The risk of breaks and fractures is our most pressing concern because of the need for invasive treatments should a break occur and could lead to loss of ambulation earlier than would otherwise be the case. This in turn would lead to many more physical and mental health issues for our son and impact his life expectancy. The increased risk of breakage also inevitably increases the risk of adrenal crisis.

We therefore want to make it explicitly clear that we wish to transition our son from his current steroid treatment to Vamorolone as soon as possible. I know I am not alone in this view. I am a member of a What's App group of dads whose son's all have DMD and have no doubt that they would want this option too.

Comment on section 3.3 (Committee discussion, Treatment options)

I would like to state that we would absolutely wish to transition to this dissociative steroid treatment as soon as possible. The current steroid treatment has been the approach for at least 20 years and its benefits and significant side effects are well known and documented.

A move to Vamorolone would benefit the whole DMD community.

Comment on section 3.4 (Committee discussion, Vamorolone positioning)

I would like to reiterate that we and the DMD community currently receiving traditional corticosteroids would absolutely wish to transition to Vamorolone (a dissociative steroid treatment).

I therefore strongly disagree with the view that 'The committee concluded that vamorolone would be likely to be used for people who have not had treatment for DMD' and the comment 'there was also interest in vamorolone for people who have had corticosteroid treatment.'. I do not feel this adequately reflects the wishes of the DMD community.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

MHRA as well as the FDA and EMA have given their medical & clinical regulatory approval to provide Vamorolone as an alternative steroid to Prednisolone and Deflazacort because of the evidence of less damage specifically to bone health and because it allows for growth. NICE view is contradictory and therefore preventing the treatment option to Duchenne children. Long term steroid use of Prednisolone and Deflazacort causes Osteoporosis. My son has Duchenne Muscular Dystrophy, he already has Osteoporosis and 3 spine fractures. He has to undergo Zoledronic acid treatment infusions at an NHS hospital and additional medication to treat his Osteoporosis. Imagine a world where this was not necessary - to not have to treat the negative side-effects of Deflazacort/Prednisolone. The clinical, physical, economic and psychological benefits far outweigh preventing the availability of the option of Vamorolone. Our Neuromuscular Consultants at NHS Evelina and GOSH are keen for our son to switch to Vamorolone as soon as possible. Our son wants to grow. He wants to attend University and study medicine. Keeping Duchenne boys healthier for longer is not only better for patients, but for the overall contribution to a better society in England. It will save cost in the long term to keep a DMD patient healthier for longer.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term'

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. I do not believe all relevant evidence has been taken into account. Evidence of cost of future hospitalisation for boys on current steroids should be factored into this. Is Vamorolone more effective in providing long term ease for boys and less frequent hospital treatments.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Absolutely not. The cost of managing long term side effects of current steroids should come into this.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. See answers previously.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

See above.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

I disagree with the decision - Boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. There has been no consideration of the positive effects on mental health of the patient, carers and family members. Given the proven safety, and known positive outcomes of this drug, (albeit it with some precision in abeyance), this would be a beacon of hope and positivity for the entire circle around the patient and indeed the patient themselves as they mature through teenage.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. The drug has strong evidential signs of benefit and has clearly been approved as safe and effective - e.g. it's prescribed in the USA. Even without complete disciplined cost effectiveness quantification, there is still a benefit, which could indeed be even higher than the estimates today.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Given the paucity of options available to DMD patients, it seems cruel and unnecessary to make this decision on the same cost effectiveness curve as other drugs (e.g. for people with self-induced or self-selected medical issues). Taking a treatment step with a lower certainty for this group, would be entirely valid.
I would propose that the drug is approved for prescription now, in parallel to conducting your "further modelling".
It's the kind and caring decision. I would propose that the drug is approved for prescription now, in parallel to conducting your "further modelling".
It's the kind and caring decision.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes. This is a disease that affects predominantly young people, almost exclusively males and largely white ethnicity. Such a decision could be easily interpreted as all of age, race and gender discrimination, as in effect it means you are steering funds away from these groups.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

Comment 1 - Clinical effectiveness

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment 2 - Adverse events

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Comment 3 - Recommendation

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

The recommendations are short sighted. The mere potential of the significant reduction of side effects of Vamorolone, as evidenced during the trials between 2015 and 2023, should be the overarching factor for the recommendation. Vamorolone gives DMD patients a chance for better bone health and growth in the long run whilst achieving the same anti-inflammatory effects. One should not forget that Vamorolone is not a new drug, it is still a steroid. NICE should progress with science and embrace the prospect of less side effects for the benefit of DMD patients and the National Health System that will have to finance the treatment of long-term side effects of conventional corticosteroids. Leading scientists believe in the effectiveness of Vamorolone; opposing progress after many years of lack of alternatives to conventional corticosteroids is not the right way forward.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

Comment 1 - Clinical effectiveness

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment 2 - Adverse events

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Comment 3 - Recommensation

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an

effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

Boys with DPD face huge side effects on the current steroids and cost the NHS more in the long run!

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows

that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Comment on section 3.4 (Committee discussion, Clinical effectiveness)

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment on section 3.6 (Committee discussion, Adverse events)

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Comment on section 3.23 (Committee discussion, Recommendation)

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. You have not directly asked any of the boys affected by DMD what they would actually want or prefer.
What about the costs of the current steroids and the issues they cause the boys on a daily basis and the cost of this.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. Not at all. You haven't considered the costs of the current issues that boys with DMD face on some of the side effects you listed - also note that you only listed some of the side effects not the huge and complete list of them.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. You are letting down an entire community of boys and their families affected by DMD.
It is approved in many other countries already, families are desperate for an alternative drug to slow down the decline of their muscles.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

You are currently refusing this drug on the grounds of disability. You imply that because the current steroids are cheaper and doing the job of slowing down the decline, the side effects for the boys are okay. They are not.

Comment on section 1 (Recommendations)

We disagree with this decision - the current steroids on the NHS have enormous side effects, and therefore an enormous impact on the boy affected and their entire family.
To simply say, it is not cost effective when you as a committee do not understand the huge and harsh implications of taking a long term steroid bring.

Comment on section 1.2 (Recommendations)

Would you accept your child having stunted growth? Weight gain? Huge behaviour problems? An increase in broken bones? No parent wants to do this to their child and yet because the treatments for DMD, as you point out, are so limited we have no choice. You are literally sitting on the one and only choice for a parent of a child with DMD, a drug with less side effects which means less issues than the current steroids and less cost for these issues on the NHS. The longer term cost value is far more beneficial.

Comment on section 3 (Committee-discussion, The condition)

Your evaluation of the condition here is extremely limited and narrow minded in thought. Nowhere in this consultation do you ACTUALLY consider the boy forced to take these steroids. Forced to accept stunted

growth, round face, broken bones, delayed puberty. Why haven't you once considered them in your consultation? The very children that will be taking this drug.
It's extremely saddening that this comes down to cost. Think about the costs of the following:
- broken bones and osteoporosis support
- behaviour and mental health needs
- delayed puberty
- stunted growth
- weight gain
How much do each of the above cost the NHS? Then multiply this for each boy affected by DMD. Which one is more cost effective now? It certainly isn't the current steroids on the market. I don't understand how you can put money above these huge issues that the boys face with the current steroids. How is that fair?
Nowhere in your consultation does it mention the huge impact your decision and the current steroids have on the families also. It is devastating to see your child suffer from the above knowing that there is now an alternative.

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. Boys with Duchenne do not have time to waste. The evidence shows that Vamorolone has less side effects that current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment options.

Comment on section 3.24 (Committee discussion, Recommendation)

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Comment on section 3.6 (Committee discussion)

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamorolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment on section 3.15 (Committee discussion)

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the

impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Comment on the draft guide consultation

I strongly oppose the decision not to recommend Vamorolone for treatment of Duchenne Muscular Dystrophy. I have two great nephews who have Duchenne and have seen first hand how devastating it is. If there is any chance that a new drug can replace the use of current steroids then it should be made available regardless. Parents should have the right to chose treatment that potentially helps their child's condition. There is no time to waste. I urge you to reconsider your decision

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. Not enough weighting or consideration given to real world evidence.

Real World Evidence in Support of licensing of Vamorolone

Whilst recognising the valid arguments made by the evaluation panel not to recommend the licensing of Vamorolone use for Duchenne sufferers, I believe not enough consideration or weighting has been given to the vital benefits to our boys and wider families which the drug will bring.

I am the grandmother of [redacted], a seven year old sufferer of Duchenne Muscular Dystrophy. He is the youngest child of my daughter, her partner and is younger brother to [redacted], my nine year old granddaughter.

Life has been hard for this young family (in common with other sufferers), following [redacted]'s diagnosis. Enormous stress and shock inevitably followed and it has radically altered the dynamic of the family. The level of

stress continues daily alongside the heartbreak of watching [redacted]'s mobility and well-being irreversibly decline. This is likely to result in the parents splitting up
due wholly to the insupportable stress brought about by differing attitudes and ways of coping with [redacted]'s condition. When this happens, my daughter will be left to lift, support and generally deal with the needs of a growing, weighty young man despite her slight build and limited strength. Added to this will be the financial hardship on herself and the two children as she will be unable to continue to work full-time and fulfill [redacted]'s growing care needs.

This is where a very real change in available medications for [redacted] would make a real difference to the family. One very real advantage would be the likely decreased future weight gain from Vamorolone use which would also impact, so importantly, on [redacted]'s sense of self-esteem, his inclusion amongst his peer group and increased ability to socialise. Current steroid medication offers parity of reduction in loss of muscle strength, but Vamorolone would ensure more likelihood of the above vital quality of life factors, in addition to financial implications for the welfare and medical state, and for both [redacted] and for my daughter and not least my granddaughter. There are of course, other real benefits from Vamorolone use of which you are aware which will bring a much-needed increase in quality of life for sufferers and their wider families.

DMD often brings with it a change in behaviour for the worse in Duchenne boys and in turn, resultant extra stress on families and time and finances for the NHS. They need and deserve all the help possible.

This plea from a concerned grandmother comes without a ream of academic evidence but with a wealth of emotional relevance and real world experience.
I would strongly urge you to reconsider your decision and recommend the licensing of Vamorolone for our boys' and families'.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Not sure they are. See above.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Financial Implications of Vamorolone use on NHS not thoroughly explored. See above

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I don’t believe it has. Look at the cost of the current side effects caused by steroids. The cost of addressing these side effects surely outweighs the cost impact of this new drug.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I don’t believe it has. Look at the cost of the current side effects caused by steroids. The cost of addressing these side effects surely outweighs the cost impact of this new drug.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Please allow this new drug. Open your minds to how revolutionary this is for the young boys in the Duchenne Community who are living with a death sentence hanging over them.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Look again at the cost of the side effects caused by the current cheaper steroid drugs that are the only drugs available to boys with Duchenne Muscular Dystrophy. DO NOT ALLOW THESE BOYS TO BE FAILED BY FINANCIAL RESTRAINTS. IT ISN'T FAIR.

Comment on draft guidance consultation

PLEASE reconsider your stance on this decision. This drug would replace steroids for boys with DMD which are currently the only ‘treatment’ available. Whilst helping to delay some of the inevitable, and catastrophic effects of Duchenne Muscular Dystrophy, Steroids create additional problems such as low bone density, adrenal insufficiency, weight gain, mood swings and place pressure on little body’s that are already fragile.

Vamorolone would offer the same benefits as steroids but without this endless list of unpleasant and life changing side effects which of course require additional support from the NHS. In the long run, the cost of the additional care caused by steroids will significantly outweigh the cost of Vamorolone. Please give these boys a chance at surviving by allowing them access to this groundbreaking drug. Denying them that opportunity is heartbreaking.

Name	[redacted]
Organisation	N/A

Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

These recommendations fail to address the huge mental health impact certain side effects of current corticosteroids. The fact is treatment options for DMD are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Vamorolone has similar short term outcomes as current corticosteroids but without impact on height and certain behavioural issues.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is so important that the impact of mental health of boys with Duchenne and their families is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We have to avoid discrimination against any group on the grounds of race, gender assignment, religion/belief, sex or sexual orientation. It would be discriminatory to limit this treatment to patients given the life expectancy of DMD. The quality of life for boys with Duchenne should always be in the forefront of a decision being made.

Comment on the draft guidance consultation

Lack of funding and effective treatment options are limited for DMD at this time so surely having access to this drug can only be a positive to improve the life of boys with Duchenne. The brutal reality is boys with DMD do not have time to waste so delaying new treatments should absolutely not be an option.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Comment on the draft guidance consultation

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment 2 - Adverse events

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Comment 3 - Recommensation

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. The report has not considered the mental health impact on the patient and their circle. An improvement in side effects and day to day life can have a significant impact on the patient and their circle. Anything that improves the day to day life of children should be given the opportunity to do so.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. The report states that the drug is not cost effective however the report also clearly states it can be beneficial for patients. Any benefit to children should be regarded as a good investment and cost effectiveness, especially considering the cost to the NHS in the long term with current severe side effects.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The report acknowledges that there is a high need for alternative treatments for DMD. Whilst the drug may not be recommended as the primary treatment option, providing as an option to healthcare providers and patients through the NHS should be authorised given the acknowledged benefit this treatment can deliver. Children should have the opportunity to access a treatment which improves their life experience, albeit within the challenges of living with DMD.

It isn't fair to make this decision based on a cost effectiveness calculation that is used for other treatments which don't have the same level of impact on the patient. It is important for healthcare as a whole and patients that

treatments are providing as an option based on more than cost. Improved treatments improves lives and provides hope.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No. This is a disease that primarily impacts on children.

Comment on the draft guidance consultation

The current treatment for DMD leads to significant side effects for patients. The proposed new treatment reduces these side effects therefore reducing the impact on the NHS (cost, time, resource) and delivering a positive impact on the patients (children suffering with DMD).

DMD is a condition that has a huge mental health impact on the patient (having an impact on their life at such a young age and coming to terms with their future) and their family and friends who are supporting the patient and processing the impact of the condition on their loved one.

Treatments for DMD are few and far between. Because the condition has such a huge impact on a vulnerable age group (and their circle), any available treatment should be seriously considered and rolled out providing there are no serious impacts of this (the drug is currently being prescribed and is seen as safe).

Cost effectiveness isn't a suitable reason to turn this down when it can significantly improve the side effects and day-to-day of children and the mental health of their circle.

However, if we must consider cost then making a treatment available which reduces potential side effects and therefore costs to the NHS should be seen as a significant positive.

Giving medical teams, care givers and parents the opportunity to make this decision for their patients and loved ones is the right thing to do and should be the foundation principle of healthcare.

Comment on section 1.2 (Recommendations), text “Because of the uncertainties in the clinical evidence and economic model, it is not possible to determine the most likely cost-effectiveness estimates for vamorolone. So, further modelling is needed, and vamorolone is not recommended”

I support the proposal for further modelling however this treatment should still be made available to medical professionals and patients in the meantime. Children are suffering from side effects that could be improved

with the new treatment. They should be given the hope and opportunity to improve their day to day life. Further modelling can help to judge whether this should be the recommended course of treatment but in the meantime families should be able to make this decision.

Comment on section 3.24 (Committee discussion, Recommendation), text "The patients and clinical experts explained that there is a high unmet need in this disease area. The committee also considered the severity of DMD and applied the 1.7 severity weighting to QALYs."

Given this need, surely it is important to offer patients the chance to try a treatment which would deliver less severe side effects. Side effects often lead to medical intervention which will cost the NHS more to address in the long term than funding the availability of vamorolone.

Comment on section 3.24 (Committee discussion, Recommendation), text "The committee concluded that there was not enough evidence to conclude that vamorolone is a cost-effective treatment option. So, it did not recommend vamorolone for treating DMD in people 4 years and over"

The committee agreed that vamorolone is an effective treatment but it isn't being recommended due to cost-effective reasoning. Given the cost to the NHS in dealing with the side effects and impact on their network, I ask that the committee reconsider their decision. I understand that resources are finite however when a safe and effective treatment becomes available for a disease that the report states has a high unmet need, severe impact on patients (children) and severe side effects (which have a significant impact on the patients and NHS resources) should be made available as a choice. There are not a lot of other treatment possibilities with DMD and patients and carers need all the support they can get to manage this condition as best as they can. Making it possible to reduce side effects for children is the humane decision.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comment on the draft guidance consultation

Comment 1 - Clinical effectiveness

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted

growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment 2 - Adverse events

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Comment 3 - Recommensation

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Once the comments have been submitted they will ask the following questions -

Has all the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group

on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Unable to comment

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Reasonable

Are the recommendations sound and a suitable basis for guidance to the NHS?

Agreed

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Not to my knowledge

Comment on the draft guidance consultation

Is Vamorolone an improved alternative to deflazacort -in the trials comparisons were between Prednisone and Vamorolone?

Given that some significant long term downsides of either prednisone or deflazacort should be avoidable on a switch to Vamorolone, the overall efficacy and safety issues will need close clinical monitoring case by case; and if the consensus view of medical profession is that the benefits outweigh risks then given the approvals granted by US and Europe health agencies it must be hoped NICE will follow suit with its approval.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I do not believe that evidence regarding brain involvement in DMD and its effect on behaviour leading to withdrawal of steroids in up to 50% of DMD patients has been adequately addressed. These patients have a worse outlook due to their inability to tolerate steroids leading to earlier onset of NIV, earlier onset of cardiac failure, worse bowel symptoms leading to hospital admission and early death. Currently corticosteroids are the only available treatment which means that these patients have no treatment option at all.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, stopping prednisolone in childhood and adolescence leads to more rapid decline and earlier use of NIV

Are the recommendations sound and a suitable basis for guidance to the NHS?

No
The efficacy of vamorolone is very similar to prednisolone and deflazacort but in terms of side effects there is a very large difference especially in terms of fewer behavioural side effects, the most common reason for steroid withdrawal

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

People with DMD who are neurodiverse due to brain involvement (learning difficulty, autism, psychiatric disorders) are a group that cannot access the benefits of steroids as they are most likely to stop due to side effects. As a consequence they have a worse prognosis
It might be argued that this group of patients with high unmet need should be given special consideration.

Comment on the draft guidance consultation

I work in adult neurology and look after 160 men with Duchenne MD, I have a background of paediatric neuromuscular disease with almost 30 years experience working with both children and adults with DMD.

46% of my adult patients take prednisolone or deflazacort, this compares with 100% of newly diagnosed DMD boys. A very small proportion of my adult cohort are steroid naive, I would guess in the region of 10%. The remainder stopped steroids in childhood or adolescence because of severe behavioural issues. We have audited our data and found that stopping steroids in adolescence results in a more rapid decline of respiratory function compared with steroid naive patients, such that by adulthood these patients have respiratory function equal to, or worse than, the steroid naive group (needing NIV around 16-18 years of age). By comparison those on steroids have much better respiratory function and do not require NIV until early to mid 20s. Thus those patients who stop steroids due to side effects need earlier onset of home ventilation (Pietrusz A et al (2023) Neuromuscular Disorders. Vol. 33, Sup 1, p.S106-S107.)

Behavioural and psychiatric issues are common in DMD, about 1/3 patients also have learning disability. We have shown that stopping steroids due to behavioural issues exacerbated by steroids leads to early death in our cohort who have neurodiversity (L. Nart et al Neuromusc disorders 2024; 35: 13-18). Thus, patients with ADHD, autistic spectrum disorders, phobias and anxiety, OCD and learning disability have a worse outlook because they cannot tolerate prednisolone of deflazacort.

Vamorolone studies have shown similar efficacy to Prednisolone and deflazacort during the course of the trials. The trials show a marked reduction in behavioural side effects and weight gain with Vamorolone when compared with prednisolone.

I think this is a very important issue to consider and I do not feel this has been adequately been addressed by the committee. The recommendation does not take into account the high unmet needs of this particular cohort. It seems irrational to not have an alternative to pred / deflazacort for those patients in whom side-effects necessitate stopping treatment when there is an available pharmacological agent. The cost of earlier NIV treatment, managing cardiac failure, acute hospital admissions for infection/ heart failure and care packages needs to be assessed against the cost of Vamorolone.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Comment on section 3.4 (Committee discussion, Clinical effectiveness)

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment on section 3.6 (Committee discussion, Adverse events)

Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with

less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Comment on section 3.23 (Committee discussion, Recommendation)

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

It seems as though no consideration is being given to the mental welfare of the young people who suffer with DMD, or the families and carers around them. When there is clearly a drug that can help, which is being used and prescribed in the USA, it would be the right thing to do to bring hope to these people and allow the drug here in the UK.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long run.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The decision should not be made on cost, especially given that this disease largely affects young people. We should be doing all we can to help give them the best life possible.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The decision is discriminating against those of a young age, predominantly males and mostly of white ethnicity.

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Has all of the relevant evidence been taken into account?

boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term

Are the recommendations sound and a suitable basis for guidance to the NHS?

boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term

Comment on section 2 (Information about vamorolone)

boys with DMD suffer huge side effects on the current steroids and as a result costs the NHS more to manage in the long term

Name	[redacted]
Organisation	N/A
Conflict	None

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

Comment on the draft guidance consultation

boys with DMD suffer huge side effects on the current steroids and as a result costs the
NHS more to manage in the long term

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Comments on the draft guidance consultation

Boys with DMD suffer huge side effects on current steroids as a result costs the NHS more to manage long term

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The recommendations fail to address the huge mental health impact certain side effects of current corticosteroid regimes bring with them. It loses sight of the fact that treatment options for Duchenne are extremely limited and this is something that has to change.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of the clinical effectiveness was clear. Vamorolone has similar short term outcomes as other corticosteroids treatments without the impact on certain elements like behavioural issues and height. The document states that it was not possible to establish a plausible cost-effectiveness estimate so it is impossible to say.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Given the devastating impact of a diagnosis and the impact on the child and family it is essential that the impact on patients and their families mental health is not brushed aside when looking at the overall effectiveness of treatment with Vamorolone vs Deflazacort/prednisone.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We must consider this treatment for patients that are either steroid naive, or wish to change their steroid regime. It would be discriminatory to limit this treatment to steroid naive patients given the limited life expectancy of DMD, boys with Duchenne simply do not have time to waste. The evidence shows that Vamorolone has less side effects than current standard of care treatments for Duchenne. Their quality of life should always be in the forefront of any decisions made regarding treatment.

Comment on section 3.4 (Committee discussion, Clinical effectiveness)

The impact on individuals and families living with Duchenne is devastating. Parents and care givers are constantly in fight or flight mode, leading to mental fatigue and exhaustion. Living with a child with DMD and watching their constant decline is heartbreaking, and steroids such as prednisone and Deflazacort bring with them behavioural issues which add to this stress. Vamrolone proves to have reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. Stunted growth is a major issue for boys with DMD. Not only are they physically weaker than their peers, they are also significantly shorter which has a huge impact on their mental health. The study shows that boys on Vamorolone are still growing at a reasonable rate compared to treatment with Prednisone/Deflazacort. This is a huge positive for boys living with DMD.

Comment on section 3.7 (Committee discussion, Adverse events)

Regarding the adverse effects and the difference between prednisone and vamorolone the fact that there are even marginal benefits to the side effects (which can be devestating in individuals who do suffer as a result of the corticosteroid treatment regime) must be a huge positive in favour of recommending varomolone.
Sadly boys with Duchenne do not have any time to waste, delaying or refusing access to treatment which proves to have a similar outcome with less side effects is simply not an option. The treatment should be available for those who wish to change their treatment regime as well as steroid naive patients.

Comment on section 3.24 (Committee discussion, Recommendation)

The Duchenne community are continuously let down by lack of funding and effective treatment options to treat their child/children. Realistically, an effective treatment/cure is not going to happen for this generation of boys with Duchenne, so allowing them access to a drug with less side effects can only be a positive to improve their quality of life.

Name	[redacted]
Organisation	N/A

Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Boys with DMD suffer huge side effects on the current steroids and this costs the NHS a lot of money to treat and prevent ongoing issues.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Boys with DMD suffer huge side effects on the current steroids and this costs the NHS a lot of money to treat and prevent ongoing issues.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Boys with DMD suffer huge side effects on the current steroids and this costs the NHS a lot of money to treat and prevent ongoing issues.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Boys with DMD suffer huge side effects on the current steroids and this costs the NHS a lot of money to treat and prevent ongoing issues.

Comment on draft guidance consultation

Boys with DMD suffer huge side effects on the current steroids and this costs the NHS a lot of money to treat and prevent ongoing issues.

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

A Single Technology Appraisal

Addendum

EAG Review of Company's Response to ACD

May, 2024

Produced by

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None

Rider on responsibility for document

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This addendum is linked to EAG report

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1. INTRODUCTION

1.1. Background

This report summarises the EAG's response to two rounds of feedback in response to NICE's Appraisal Consultation Document (ACD, March 2024) following the first Appraisal Committee meeting for vamorolone for treating inflammation associated with Duchenne muscular dystrophy [ID4024].

The first round of feedback was the company's revised base case analysis. The new model adopted the committee's preferred assumptions but also introduced several additional revisions that were not requested. The EAG reviewed and critiqued this revised base case analysis.

Following EAG's initial response to the revised base case, NICE requested that the EAG turn its attention to a patients group survey delivered by Muscular Dystrophy UK and Action Duchenne – also post the ACD. NICE asked that the EAG covered the following queries:

- Briefly summarise key findings from the survey.
- Interpret the modelling methods, assumptions, and results of the company's updated model in light of the survey.
- Further elucidate the EAG's questions and concerns around adverse event modelling.
- Comment on the company's change from using health state utilities taken from the BOI study (Evans et al.[1]) to those utilities from Landfeldt et al (2023).[2]

1.2. This report

This report brings together the EAG's responses to the two rounds of feedback described above.

Section 2 describes the EAG's response to the company's revised base case following the ACD. The section summarises the changes made by the company in response to the committee's preferred assumptions, as well as a critique of the additional changes made by the company.

Section 3 summarises the patient groups' survey – its questions and main findings, placed in the context of the clinical evidence. The EAG then describes how adverse effects (AEs) have been modelled in light of the survey.

Section 4 summarises the two main sources of utilities that have been used during the process – Evans et al. (2020)[1] (alternatively known as the BOI study) and Landfeldt et al (2023).[2] The company switched from originally using Evans to using Landfeldt post ACD.

Finally, Section 5 provides the EAG's corrected company revised base case results, and the EAG's updated base case and scenarios.

2. EAG RESPONSE TO COMPANY'S SUBMISSION FOLLOWING ACD

2.1. IMPLEMENTATION OF COMMITTEE PREFERRED ASSUMPTIONS

This section presents the EAG critique of company's implementation of the committee's preferred assumptions in the revised economic model (version 3.0). A summary is provided in Table 1.

1. **Fully incremental analysis with prednisone and deflazacort as individual comparators:** The company's revised model presented fully incremental analysis for the deterministic analysis. However, for the probabilistic analysis the model was still run in a pairwise manner (i.e. vamorolone was compared with prednisone first and then compared with deflazacort and the results were presented for each individual comparison). Ideally, a separate Markov trace for prednisone and deflazacort could be replicated and the model programming should have been altered to run the probabilistic analysis in a fully incremental manner. However, this was not implemented in the company's revised model. The probabilistic analysis results presented in the submission (v 3.0) also lacked face validity. For instance, the deterministic total QALYs for vamorolone was [redacted] (as reported in Table 37 of company's ACD response v3.0) while the probabilistic total QALYs was [redacted]. The EAG noted that this was due to reporting error, which was subsequently fixed.

2. **Consider difference in muscle function outcomes between treatments based on VISION-DMD:** The EAG highlighted in the ACD that vamorolone was less effective than prednisone for all muscle function outcomes, casting doubt on the company's claim of vamorolone's comparable efficacy to prednisone. In line with the committee's preference, the company's revised model incorporated a scenario for vamorolone with reduced efficacy compared to prednisone and deflazacort. The reduced efficacy (10%) was applied to the HR of progression for vamorolone, thus speeding up the progression of patients through the modelled health states. However, no reasoning was presented for a 10% reduction in efficacy, and this appeared to be an arbitrary judgment. The EAG conducted an analysis of differences in point estimate outcomes using data from five muscle function outcomes reported in VISION-DMD. This suggested a reduction in efficacy of 32%, when using vamorolone instead of prednisone. The EAG recognised this was a crude analysis, and as a compromise considered the approximate midpoint of

20% to be plausible and conducted a scenario on this basis (see Section 5 for further details).

3. **Plausible assumptions for stopping treatment with vamorolone:**

Time on treatment

The committee considered in the ACD that the company's extrapolation of time on treatment with vamorolone have been substantially underestimated and did not align with the claim of vamorolone's superior safety profile. The committee also noted that the EAG's assumption that the time on treatment with vamorolone would be similar to that of deflazacort was preferable, though highly uncertain. In the revised model, the company incorporated the EAG suggestion and assumed vamorolone discontinuation to be the same as deflazacort as per the CINRG data. The committee also indicated that alternative sources of data such as the NorthStar registry (UK DMD dataset) could be consulted. The company attempted to explore the NorthStar registry dataset as per the committee's suggestion and submitted a data request. However, they did not receive the vamorolone 'time on treatment' data in time for inclusion in the model.

Stopping rule

The committee indicated in the ACD that there was no clear clinical rationale to recommend any appropriate stopping rule. However, the company's revised model included a stopping rule for vamorolone when patients commence night-time ventilation. The EAG excluded this assumption in line with the committee's preference in its analyses. Note that no stopping rule was applied for the comparator corticosteroids (i.e. patients continued all treatments until death unless discontinued). The EAG also had the following response from one of their clinical experts: *"Our practice is to continue steroid. If the main advantage of vamolorone is that it does not impair growth, growth will usually have completed by the time night-time ventilation is started, so there may not be an advantage in using vamorolone rather than prednisolone. However, if patients have been on vamorolone they may be very reluctant to change."*

4. **Plausible assumptions following dose reductions for vamorolone and SoC:**

In its report prior to AC1,[3] the EAG noted inconsistent handling of efficacy post dose-reduction between vamorolone and prednisone or deflazacort. The committee recommended that all the treatments should be modelled the same way in terms of their

effectiveness and safety profile following dose reduction. In the revised model, the company addressed this concern in the vamorolone Markov trace by adjusting the proportion of patients in each health state using the proportion on treatment receiving full efficacy by deriving the transition probabilities as an average for treatment and no-treatment, consistent with the approach for prednisone or deflazacort.

However, a hazard ratio-based approach to adjust the efficacy for down-titrated patients was introduced into the revised model. The hazard ratio was derived from FOR-DMD[4] based on which a two-fold increased risk ([redacted]) for losing the ability to stand was observed in patients who had to reduce the dose of daily prednisone or deflazacort due to side effects. This HR was applied to the SoC transition probabilities speeding up the progression while a HR = 1 was applied to vamorolone in the company's base case. The issue with this approach was that the ability to stand was relevant only from health states HS1 to HS3. However, it was applied across all health states, which might overestimate the progression of patients with SoC treatments. The EAG also noted that the model results were sensitive to the approach being chosen, i.e. with the original approach (% efficacy reduction for steroids following dose reduction as per clinical opinion), the ICER increases substantially (>100%). Therefore, without a credible clinical opinion EAG was unable to weigh appropriately one method over the other, given both methods suffer some limitations and have associated uncertainties. Hence, the EAG's preference is to maintain the original percentage efficacy reduction upon down-titration as per the original submission, given the issue was more to do with the implementation rather than the methodology itself.

For the prednisone and deflazacort arms in the company's revised model, they applied a reduction in AEs when people down-titrate from full dose as per FOR-DMD. The reduction applied was specific to the adverse event reported – i.e., the specific change in behavioural issues seen in the prednisone arm in FOR-DMD after dose reduction was applied to behavioural issues in the prednisone arm on dose reduction in the economic model. However, this methodology was not used for the vamorolone arm of the model. Instead, the mean reduction in adverse events after dose reduction in FOR-DMD, which was 18% (i.e. 82% of the full dose), was applied to all of the vamorolone AEs after dose reduction in the model. The EAG's clinical experts did not consider it reasonable that all adverse events would be reduced by the same factor after a reduction in dose. This can

be seen in the contrasting reductions in AEs seen after dose reduction in FOR-DMD. Also, the EAG did not consider it appropriate that FOR-DMD adverse event data was applied asymmetrically to the prednisone and deflazacort treatment arms as compared to the vamorolone treatment arm – i.e., adverse event specific reductions for prednisone and deflazacort, and a flat reduction of 18% for vamorolone. As previously stated, the EAG do not consider it appropriate to use a flat reduction of 18% to all AEs after dose reduction. If FOR-DMD data are going to be used in this analysis it would be more appropriate to apply adverse event specific changes to the vamorolone arm in the model, as was done for the prednisone and deflazacort treatment arms. However, given the short time-period of this assessment, the EAG have excluded this assumption in its analyses.

Finally, the EAG noted that in the revised company's submission base-case, irrespective of the vamorolone dosage, people would receive the same level of efficacy with vamorolone, which is not consistent with the reduced efficacy upon down-titration used for prednisone and deflazacort. However, the company did present a scenario where they used a 7% reduction in efficacy upon down-titration to vamorolone 4 mg/kg. The reduction in efficacy by 7% was based on their PKPD model. However, the EAG was concerned that this was not based on study data in which people received vamorolone at 4 mg/kg but was based on extrapolations from 166 boys who received vamorolone at 0.25, 0.75, 2 and 6 mg/kg across the pivotal trials. Given this small sample size and lack of direct data in people using vamorolone 4 mg/kg, the EAG do not consider estimates of efficacy derived from the PKPD analysis to be credible. Given the lack of credible efficacy data for people using vamorolone 4 mg/kg, the EAG has not implemented any efficacy reduction.

5. **Excluding growth hormone (for stunted growth) and non-reference case costs:** In the revised model, the company excluded the growth hormone costs aligned with the committee preference. However, the company added the costs of two endocrinologist visits (first and follow up) towards the management of stunted growth. The EAG was unable to cross-validate this assumption with the clinical experts given the time constraints. This is not influential on the ICER but the EAG considers it may be worth seeking clinical validation. Given the uncertainty associated with this assumption, the EAG has excluded it from its analyses.

6. **QALY weight of 1.7 applied to patient QALYs only:** The EAG noted that the company's revised base case model applied a QALY weight of 1.7 to only patient QALYs and that this is now consistent with the requirements of the NICE manual.[5]

Table 1. EAG critique of company's implementation of committee preferred assumptions.

	Committee preferred base case assumptions and scenarios	Whether implemented in company's updated base case?	Whether the implementation is appropriate (i.e. holds face validity?)	EAG comments
Committee preferred assumptions				
1	Consider prednisone and deflazacort as individual comparators in a fully incremental analysis (FIA)	Partially (deterministic analysis correct, errors in PSA).	Deterministic results appear correctly implemented. However, the PSA results lacked face validity (instead of total QALYs reported only patient QALYs for vamorolone in Table 38-39 of company ACD response v3.0).	Individual comparisons are now made vs steroids however it is still not 100% FIA (and no separate markov trace for prednisone and deflazacort in the model). PSAs have been run separately for vamorolone vs prednisone or deflazacort in a pairwise manner and contained some errors which was subsequently fixed by EAG (see Section 5).
2	Considering a difference in muscle function outcomes between treatments based on VISION-DMD	Yes	Company's revised model provided cost-effectiveness scenarios which assumes a difference in muscle function outcomes between treatments based on VISION-DMD results (i.e. vamorolone 6mg/kg was assumed to have lower efficacy than prednisone 0.75mg/kg and deflazacort 0.9mg/kg). To test this, reductions of 5% and 10% versus each steroid were considered as scenarios. In addition, a scenario assuming a reduced efficacy for vamorolone 4mg versus vamorolone 6mg was also implemented, with a hazard ratio of 1.075. EAG did not find any issues with the implementation.	This scenario does not have a large impact on the ICER. As expected, a reduction in health state QALYs and increase in health state costs was observed for vamorolone. However, faster progression due to reduced efficacy resulted in reduced on treatment proportion over time leading to lesser treatment costs with vamorolone. The net effect is that the ICER decreased slightly. EAG has included 20% reduction in efficacy in its analyses.

	Committee preferred base case assumptions and scenarios	Whether implemented in company's updated base case?	Whether the implementation is appropriate (i.e. holds face validity?)	EAG comments
3	Plausible assumptions for discontinuing treatment with vamorolone (with potential longer time on treatment with vamorolone to match its better safety profile claim)	Yes	Aligned with EAG's preference company has assumed vamorolone discontinuation to be the same as deflazacort CINRG data but the UK NorthStar registry data has not been implemented in the model (which was mentioned in the ACD as one of the potential alternative data sources).	Company's revised model did not include UK NorthStar data (though dropdown option exists in the model, the linked data table was noted to be blank).
4	All treatments modelled the same way in terms of their effectiveness and tolerability after dose reduction, when considering no difference between vamorolone and prednisone or deflazacort	Yes	Company has updated the vamo Markov trace to adjust for proportion of patients undergoing dose reduction. However, introduced a hazard ratio-based approach (in addition to previous approach) using FOR-DMD data, based on which two years after reducing the dose, a two-fold increased risk for losing the ability to stand is observed in patients who had to reduce the dose of daily prednisone or deflazacort due to side effects in the first 12 months, compared with patients who could maintain the recommended dose at least 12 months. In addition, loss of ambulation owing to non-vertebral fractures has been included which provides some advantage for vamorolone over steroids and results in slightly higher health state QALYs for vamorolone.	The HR of [redacted] has been applied to all health states and not just to HS1 to HS3 (the health states where patient's ability to stand is relevant). EAG considered equal efficacy and tolerability assumptions for all treatment pre- and post- dose reductions in its base case and in line with committee's recommendation considered a scenario of reduced efficacy and tolerability following dose reductions for all treatments.
5	Exclude growth-hormone and non-reference case costs	Yes	Yes, however included two endocrinologist visits costs (first and follow up).	Growth hormone and non-reference case costs were excluded from the company's revised base case (though included endocrinologist visits costs, the impact of which on the ICER was minor).

	Committee preferred base case assumptions and scenarios	Whether implemented in company's updated base case?	Whether the implementation is appropriate (i.e. holds face validity?)	EAG comments
				Given it is not clear whether 2 endocrinologists visits might be needed for all patients having stunted growth and EAG unable to cross-validate this assumption with clinical experts due to time constrains, EAG has excluded in its base case.
6	Use a QALY weight of 1.7 applied to patient QALYs only	Yes	Yes	1.7 weight applied to patient QALYs only as per committee preference
Additional scenarios requested by the committee				
7	More robust modelling of adverse events, including the severity of adverse events, how behavioural issues are modelled and the impact of adverse events over time	Yes	Adverse events are split separately now for prednisone and deflazacort (it's more granular for steroids now based on CINRG data). Also, for vamorolone 18% reduction in AEs is applied based on FOR-DMD data (which is an average across all AEs) while the event specific rates are applied for corticosteroids. The EAG noted that the company's revised model assumed that: mild AE disutilities = 0.25 * moderate/severe AE disutilities. However, no rationale was provided for this assumption. Following the clarification questions, the company responded that this was a proxy approach for mild AE disutilities, given the paucity of data. As this assumption is arbitrary and introduces uncertainty, an exploratory scenario was run by the EAG with 50% (i.e. mild AE	Given the time constrains, the EAG was unable to do a full QC of all the changes done in terms of AEs. However, would like to note that the EAG spotted potential issues which might affect the validity of AE costs and calculations.

	Committee preferred base case assumptions and scenarios	Whether implemented in company's updated base case?	Whether the implementation is appropriate (i.e. holds face validity?)	EAG comments
			disutilities = 0.50 * moderate/severe AE disutilities) to test the impact on the results. The EAG further noted a lack of face validity regarding mild AESI behavioural issues being higher in the vamorolone arm. Following a clarification question, the company reported that this was based on VISION-DMD mild AESI rates. These were calculated as the difference between total AESI rates and the moderate/severe AESI rates. As prednisone had a significantly higher rate of moderate/severe AESI and a more minor increase in total AESI versus vamorolone, this led to a larger proportion of AESI for vamorolone being mild.	
8	More robust modelling of health-related quality of life, including health state utility values, and patient and carer adverse event disutilities	No	Committee's concern of how behavioural issues and stunted growth disutilities are applied in the model does not seem to have been addressed as the updated model uses higher than previous duration of 6 months. Also, 2 carers were applied for more severe health states (HS4 to HS8).	The company has increased the duration of behavioural issues from 6 to 18 months. A similar extrapolation is made for stunted growth. Company has assumed patients are at risk of behavioural issues for life; clinical advice to the EAG disagreed with this. Also, the assumption of two carers for severe health states might be over estimating carer QALYs.
9	Updating the economic model to account for the potential of treatment sequencing, to reflect the treatment pathway for DMD	No	-	The updated model does not consider potential for treatment sequencing.

2.2. IMPLEMENTATION OF ADDITIONAL ASSUMPTIONS IN COMPANY'S BASE CASE

This section presents the EAG critique of additional assumptions (other than the committee preferred assumptions) implemented in the company's revised model (v3.0), in Table 2. The EAG has reviewed these and considers some to be reasonable. However, the EAG considers a number to be lacking in sufficient justification. There is disagreement in terms of the use of an alternative source for health state costs, the modelling of behavioural issues, number of caregivers, number of patients receiving spinal surgery, loss of ambulation following long bone fracture, and application of hazard ratios to the no treatment arm.

In terms of how the adverse events were modelled, the EAG noted the following:

- Disutilities of mild AEs were calculated assuming they were 25% of moderate/severe AEs (see Table 1). This approach appears to be arbitrary and without any justification. To provide some idea about the associated uncertainty, the EAG has tested (an equally arbitrary) 50% as a scenario.
- There were also concerns around the disutility source used for behavioural issues and the value applied. Based on clinical opinion received, the EAG has restricted the application of behavioural issues disutilities only to boys aged 4-12 as applied in its base case (see Table 2 for further details).

Table 2. EAG critique of additional assumptions (other than committee preferred assumptions) implemented in company's revised base case

	Additional assumptions implemented in company's updated base case	Whether EAG agree? (Yes/No)	EAG comments
1	Mortality capping using Broomfield et al. 2021	Yes	There were limitations with the mortality extrapolations in the natural history model (NHM) leading to overestimation of survival as highlighted by the committee. The EAG noted that the survival probabilities were still higher with Broomfield et al. 2021, and higher yet without capping. For instance, with capping, the proportion surviving at 50 years for SoC was 18%, whereas without capping it was 23%. Therefore, the EAG has included capping in its analyses.
2	Longer time horizon of 95 years	Yes	A small proportion of patients (15%) were still alive at the end of 50-year time horizon in the model. Therefore, extending the time horizon might be reasonable.
3	Health state costs based on Landfeldt et al 2017	No	The Committee did not raise concerns with the health state costs used. The first iteration of company's updated model had health state costs based on the BOI study (Evans et al 2020), which aligns closely with Project HERCULES and was reviewed by its steering committee. Since the vamorolone model structure is based on Project HERCULES natural history model (NHM) for DMD, the BOI study represents health states in line with the NHM. However, the health states in Landfeldt et al is not aligned to the Project HERCULES NHM. Moreover, the company's original submission stated: "A burden of illness (BOI) study, informed by a Delphi panel, collected HRQL data for patients and caregivers using a preference-based measure. The NICE reference case hierarchy states a preference for public preferences using a choice-based method. Also, the BOI study is informed by patients and carers based in the UK and is therefore suitable for UK HTA submission".
4	Growth stunting disutility increased to a duration of 8 years	Yes	The company has cited updated clinical opinion as a reason to change the duration. Expert opinion to the EAG agreed with this.
5	Behavioural issues disutility increased to 18 months	Partially	The company has cited updated clinical opinion as a reason to change the duration from 6 to 18 months. The EAG's clinical expert confirmed this was

	Additional assumptions implemented in company's updated base case	Whether EAG agree? (Yes/No)	EAG comments
			reasonable. However, the EAG notes that patients are assumed at risk of increased behavioural issues for life. Clinical advice to the EAG was that all boys with DMD are likely to experience behavioural issues, and that steroids will increase their severity. However, this is only plausible from starting steroids (assumed age 4 in the model) to approximately age 12; continuing behavioural issues beyond this age will not be due to steroids. The EAG's base case therefore limits the risk and thus impact of enhanced behavioural issues to ages 4-12 only. Furthermore, the EAG has concerns with the assumed disutility applied to behavioural issues. The company was unable to identify directly relevant estimates, and neither was the EAG. The source used by the company relates to the impact of side effects from antiepileptic drugs in an elicitation study.[6] Whilst the study was well conducted, side effects were simply defined as 'mild/moderate/severe', without further detail; the EAG was unable to locate a reference to 'irritability and aggression' quoted in the company submission (Table 56). The company assumed behavioural issues were equal in severity to severe side effects from anti-epileptic drugs (disutility of 0.12). In the absence of evidence, the EAG adopted a conservative approach assuming a disutility equal to moderate side effects (0.06).
6	Two caregivers assumed from loss of ambulation until death	No	The Committee did not state in the ACD that one carer per person was unreasonable. Furthermore, the Landfeldt et al 2017 model also uses only one carer per person for all health states.
7	Number of patients receiving spinal surgery is based on cumulative loss of ambulation and discontinuation	No	No justification was provided by the company for this change from the original model.
8	Patients may lose ambulation due to the occurrence of a long bone fracture	No	The EAG was concerned that this modification from the original model lacked justification. Clinical expert advice to the EAG was that, in the majority of cases, people with long bone fractures recover and become ambulatory again. However, they did note that in people who sustain a fracture, the recuperation period tends to make them weaker, leading to even more precarious ambulation. There are also a minority of cases where people who were already close to losing ambulation prior to the fracture occurring, do not regain ambulation after recovery from the fracture.

	Additional assumptions implemented in company's updated base case	Whether EAG agree? (Yes/No)	EAG comments
9	Bisphosphonates costs refined in line with Joseph et al. (2019)2 to reflect real-world clinical practice	Yes	The EAG considered this to be reasonable.
10	Cataracts included with associated costs and disutilities (1 month disutility)	Yes	The EAG noted that the company has provided additional evidence for including cataracts and it seems broadly reasonable.
11	Average dose amended in line with average dose by age based on CINRG for prednisone and deflazacort	Yes	Given CINRG data has been used for discontinuation, the EAG considers this assumption to be reasonable.
12	Hazard ratios applied to no treatment arm set to 2.41 for all health states	No	No clear rationale for using higher HR for all health states. Therefore, the EAG prefers to retain the original base case.
13	Include loss of ambulation due to fracture	No	Excluded proportion of patients with non-vertebral fractures losing ambulation in EAG analyses, as inclusion lacks appropriate justification.
14	Health state utilities changed from BOI study to Landfeldt et al 2023	No	See Section 4 for details.

2.3. COMPANY'S REVISED BASE CASE (ACD VERSION VS LATEST VERSION FOLLOWING ACD)

Table 3 below, presents the differences in terms of key base case assumptions in company's original submission at ACD compared to company's revised submissions following ACD.

Table 3. Company's key base case assumptions (original vs revised submission)

No.	Original base case assumptions at ACD	Revised base case assumptions following ACD (v3.0)
1	Vamorolone discontinuation same as prednisone	Vamorolone discontinuation same as deflazacort
2	Different efficacy assumptions following dose reduction for vamorolone and SoC • Percentage reduction in efficacy applied only for SoC upon down-titration based on clinical opinion	Different efficacy assumptions following dose reduction for vamorolone and SoC • HR based approach added for efficacy reduction following down-titration for SoC • Reduction in AEs following down-titration based on FOR-DMD for vamorolone and SoC • Different hazard ratio assumptions applied to no treatment arm
3	Health state costs and utilities based on BOI study[1]	Health state costs based on Landfeldt et al 2017[7] and utilities based on Landfeldt et al 2023.
4	Growth hormone and non-reference case costs were included	Growth hormone and non-reference case costs were excluded; 2 endocrinologist visit costs included for stunted growth
5	1.7x QALY weight applied to both patient and carer QALYs	1.7x QALY weight applied to only patient QALYs
6	No stopping rule applied	Stopping rule applied for vamorolone while starting night-time ventilation
7	No complex PAS	Complex PAS turned off in the model
8	Time horizon = 50 years	Time horizon = 95 years
9	Mortality not capped with Broomfield et al 2021	Mortality capped with Broomfield et al 2021[8]
10	Loss of ambulation due to non-vertebral fractures not considered	Loss of ambulation due to non-vertebral fractures included
11	Disutiliies duration: • Behavioural issues: 6 months • Stunted growth: 1 year • Spinal fusion surgery: 1 year	Revised disutilities duration: • Behavioural issues: 18 months • Stunted growth: 8 years • Spinal fusion surgery: 2 years
12	Number of carers per person: 1 for all health states	Number of carers per person: 1 for HS1 to HS3; 2 for all other health states

3. THE PATIENT GROUPS' SURVEY

3.1. Summary of key findings from the patient groups' survey

The patient groups' survey was carried out by Muscular Dystrophy UK and Action Duchenne, UK charities focusing on muscular dystrophy and related conditions.

The survey was performed using Survey Monkey. Respondents were members of the Duchenne community between 15 April 2024 and 21 April 2024. Seventy-six people took part in the survey: 7 respondents (9.2%) had DMD, 61 respondents (80.3%) were a parent of a child with DMD, 6 respondents (7.9%) were a carer for someone with DMD, and 2 respondents (2.6%) stated wider family member or friend association with DMD.

The survey asked five questions on the adverse events (AEs) linked to corticosteroid treatment for people with DMD. Responses to four of the questions were on a five-point scale, where a low score indicated no effect, and a high score indicated a strong effect. The survey also presented moving testimony of people with DMD and their carer's experiences of corticosteroid treatment. The report highlighted that the families who responded had many similar experiences of corticosteroid treatment and the effects of its AEs on day-to-day activities.

A summary of each question is provided below.

Question 1: Asked about the severity of side effects and found that stunted growth had *moderate severity* whereas most of the other AEs, including behavioural/emotional changes, delayed puberty, risk of fractures, weight gain, and osteoporosis had *some severity*.

Question 2: Focussed on the interference of corticosteroid AE with day-to-day activities. In this case behavioural/emotional changes, risk of fractures, and osteoporosis *moderately interfered* with day-to-day activities, whereas there was *minimal interference* from weight gain, stunted growth, and delayed puberty, among others.

Question 3: Covered behavioural/emotional changes and found that 64.7% of respondents judged behavioural issues to occur *often* or *all the time.*

Question 4: Focussed on how much quality of life could be improved through a reduction in each adverse event. The survey found that a reduction in weight gain, stunted growth, osteoporosis, risk of fractures, or behavioural/emotional changes would lead to *moderate improvements* in a person with DMD's quality of life.

Question 5: Asked respondents if they would like to share anything else about their experience of corticosteroid treatment. Thirty-six respondents took this opportunity – two of the most detailed responses were provided, both of which provided a very moving testimony to living with the condition and the challenges of balancing the benefits of treatment with the impact of AEs.

In summary, the patient survey found that stunted growth, behaviour problems, weight gain, risk of fractures and osteoporosis, were the critical AEs for people with DMD and their carers.

It was instructive to relate these patient survey responses to the safety outcomes reported in the VISION-DMD trial, where vamorolone 6 mg/kg/day was compared to standard of care (prednisone 0.75 mg/kg/day).

VISION-DMD was a small trial with each treatment arm containing about 30 children. The primary trial period was 24 weeks. Therefore, the EAG noted that AE outcomes were based on short follow-up and were uncertain due to low event rates. However, with that uncertainty in mind, the EAG understood there may be benefits for people on vamorolone over prednisone for stunted growth. This conclusion was drawn from the children's height z-scores at 24 weeks and 48 weeks, but it was notable that no children were assessed to have stunted growth during the trial.

All children with DMD are at increased risk of behaviour problems. This was seen in VISION-DMD as there were children with behaviour problems in all four treatment arms. However, there were fewer children with behaviour problems in the vamorolone arms as compared to the prednisone arm. This was a small difference and, as stated in the EAR, prednisone treatment was associated with increased behaviour problems.

The final three critical adverse events highlighted in the patient survey were weight gain, risk of fractures, and osteoporosis. Weight gain was reported in VISION-DMD, and there was an increased risk of weight gain following vamorolone 6.0 mg/kg/day as compared to prednisone, though event rates were small. The trial was of too short duration to report reliably on risk of fracture; neither did it report osteoporosis.

In conclusion, the VISION-DMD trial was too small and too short in duration to be considered strong evidence of vamorolone's relative safety in comparison to prednisone. However, there were signs that treatment with vamorolone may lead to fewer people with stunted growth and fewer behaviour problems, compared to treatment with prednisone. It was unclear if there were

any benefits or harms for vamorolone versus prednisone for weight gain, fractures, or osteoporosis.

The EAG also noted in the EAR that there was no direct evidence comparing AEs in people on vamorolone versus deflazacort. and the EAG understood that deflazacort had a different safety profile to prednisone. For example, fewer behaviour problems but increased risk of stunted growth and extremely delayed puberty.

3.2. Interpretation of AE modelling in light of the patient groups' survey

While the patient groups' survey provided valuable insight into the relative effects of AEs associated with steroids and their impact on daily living, it did not provide any point estimates which could be used as inputs directly into the model (such as AE rates, disutilities etc.). The key concern with respect to the modelling of vamorolone adverse events is whether the reduction of side effects observed in the VISION-DMD trial would be sustained in the long-term. This question could not be answered by the patient groups' survey.

Nevertheless, the EAG attempted to corroborate some of the key inputs used for the modelling of steroid AEs with that of the survey.

- Adverse events which have the largest impact on the cost-effectiveness results – namely behavioural issues and stunted growth – also have a high rating in the survey in terms of severity and interference with daily activities (Table 4). In this case, therefore, the patient survey results support the approach used in the model.

- The survey reports that 61.1% of people with DMD experienced behavioural issues either 'often' or 'all the time'. The remaining 39.9% experienced it only 'some of the time', 'rarely' or 'not applicable' (assumed to be 'not at all'). This is, however, not reflected in the company's model, where there is no grading of frequency. Instead, the QALY loss per event for behavioural issues (calculated as a product of disutilities and the duration of the event) was applied to all people with DMD at the same level. The EAG base case partly accounted for this by applying behavioural issues only for boys aged 4-12, in line with the clinical opinion received following ACD.

Table 4. Stunted growth and behavioural issues (model inputs vs patient survey)

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

4. HEALTH STATE UTILITIES

Two utility value sources have been used and discussed during this appraisal process. The company changed their source of utilities from the BOI study to Landfeldt et al.(2023) post ACD.

Utility values based on the BOI study (Evans et al. 2020[1]): Patient utility values from the BOI study (which was part of project HERCULES) used a condition specific DMD-QoL measure. The EAG noted that an early ambulatory health state utility value was not available in the BOI study and therefore assumed to be the same as Landfeldt et al 2017.[7] The committee raised concerns about the face-validity of these utility values, given that some of the more severe health states utility values were higher than earlier (less severe) health states. While acknowledging these concerns, the EAG noted that the values were broadly similar despite being slightly lower – for instance, the patient utility value for 'HTMF, night-time ventilation' was 0.53, while for 'No HTMF, night-time ventilation' it was 0.52. However, the company submission (original as well as the updated one following ACD) did not provide any explanation in this regard.

Utility values based on Landfeldt et al 2023[2]: Landfeldt reported the EQ-5D-3L values (as well as values based on other measures such as HUI and Peds-QL) from an international cohort of patients, where 58% of participants were from the United States or the United Kingdom (combined percentage reported in the paper). The EAG noted that US tariffs were used to convert the responses to an index value,[9] which might limit generalisability to a UK context.

Given there were limitations associated with both sources, the EAG did not have a strong preference for one over the other. Also, the EAG noted that changing the source of utility values was not influential on the cost-effectiveness results. However, as the EAGs base case health state costs were derived from the BOI study and given the modelled health states align closely to that of BOI study, the EAG has updated its base case to include BOI utility values for consistency.

Noting the committee's face validity concerns, the EAG also included a scenario that assumes BOI utility values to be the same for 1) 'no ventilation' and 'night-time ventilation' health states and 2) 'transfer' and 'late ambulatory' health states (Section 5,Table 8).

5. REVISED EAG BASECASE AND SCENARIOS

This section presents the EAG corrected company base case, EAG preferred base case assumptions (Table 6) and its results (Table 7) and EAG scenarios (Table 8).

As mentioned in Section 2.1, The PSA results presented in the company's revised submission (v3.0) lacked face validity and there was a huge difference between the deterministic and probabilistic costs and QALYs. EAG subsequently fixed the PSA to be functional, and the corrected results are presented in Table 5. Also, please note that the deterministic results presented in the company submission had only patient QALYs instead of total QALYs which has also been corrected.

Table 5. EAG-corrected company revised base case results

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

Table 6. EAG base case assumptions following ACD

S.No	Revised EAG base case assumptions following ACD
1	Vamorolone discontinuation same as deflazacort*
2	Reduced vamorolone efficacy (20%) to account for numerical differences in muscle function outcomes as per VISION-DMD
3	Efficacy assumptions following dose reduction for vamorolone and SoC • Equal efficacy and tolerability applied for all treatments following dose reduction including mild AEs (i.e. no reduction in efficacy or AEs assumed) • Hazard ratio assumption for no treatment arm set to base case
4	Health state costs and utilities based on BOI study[1]
5	Growth hormone and non-reference case costs were excluded; 2 endocrinologist visit costs excluded for stunted growth
6	1.7x QALY weight applied to only patient QALYs*
7	No stopping rule applied for vamorolone (i.e. vamorolone continued until death) in line with SoC
8	Time horizon = 95 years*
9	Mortality capped with Broomfield et al 2021[8]*
10	Loss of ambulation due to non-vertebral fractures excluded
11	Revised disutilities duration: • Behavioural issues: 18 months (applied to ages 4 to 12, at a disutility of .06) • Stunted growth: 8 years* • Spinal fusion surgery: 1 year
12	Number of carers per person: 1 for all health states

* included in company's updated base case

Table 7. EAG revised base case results (updated)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)
EAG corrected company base case					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced vamorolone efficacy (20%) for muscle function outcomes*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No reduction in efficacy or AEs following dose reduction for all treatments (including mild AEs)*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utilities as per BOI study*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state costs as per BOI study*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endocrinologist visit costs excluded for stunted growth*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No stopping rule for vamorolone*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of ambulation due to non-vertebral fractures excluded*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of carers per person: 1 for all health states*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Behavioural issues disutility (0.06) applied for boys 4-12 years old*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal fusion surgery disutility duration (1 year) *					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (deterministic) *includes all the changes above*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative EAG base case results (probabilistic) *includes all the changes above*					
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*changes applied individually

Table 8. EAG scenarios

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (fully incremental)	% change from EAG corrected company base case
EAG corrected company base case						
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AESI disutilities = 0.5* moderate/severe AESI disutilities						
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utilities as per amended BOI study values						
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC efficacy following dose reduction based on original percentage efficacy reduction						
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced efficacy following dose reduction for all treatments (40% reduction applied to vamorolone same as SoC)						
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule applied to both vamorolone and SoC (while starting at night-time ventilation)						
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Single Technology Appraisal

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

EAG critique & addendum – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG critique and addendum to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 29 May 2024.** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Scenario results - reduction in efficacy and AEs for down-titration

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 4, page 14 (Addendum): The results for "*No reduction in efficacy or AEs following dose reduction for all treatments"* are incorrect.	The EAG should update the results to give the correct ICER of [redacted], instead of [redacted].	The EAG have presented incorrect results meaning the reader is misinformed on the impact of this scenario.	We thank the company for their review of this issue. The EAG is unclear how the company derived the ICER of [redacted] (i.e. it has not been made explicit which settings were altered). However, the EAG notes that the result as currently presented for this scenario included the exclusion of loss of ambulation (LOA) due to non-vertebral fractures. Given that this is presented as a separate scenario as part of the EAG's preferred assumptions, the result of this scenario is updated in Table 7 to not include the exclusion of LOA from non-vertebral fractures, resulting in an ICER of [redacted].

Issue 2 Muscle function outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Point 2, Page 4 (Final critique): *"The committee highlighted in the ACD that vamorolone was less effective than prednisone for all muscle function outcomes."* The Committee did not state that vamorolone is less effective than prednisone for all muscle function outcomes but, rather that vamorolone has a numerically lower, and not statistically significant, outcomes across all muscle function outcomes compared to prednisone.	The EAG should update their language in line with the data to state that 'vamorolone has numerically lower, but not statistically significant, outcomes across all muscle function outcomes compared to prednisone.'	Stating that vamorolone was less effective in muscle function is a misinterpretation of the data, given that the results are not statistically significant.	As the trial was under-powered for detecting a difference between the prednisone and vamorolone 6 mg/kg trial arms, the EAG did not consider statistical significance to be probative. However, it is acknowledged that this is the EAG's interpretation of these data and the statement in the report has been altered to clarify this: "The EAG highlighted in the ACD that vamorolone was less effective than prednisone for all muscle function outcomes."

Issue 3 Time on treatment data availability

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Point 3, Page 5 (Final critique): “The committee also indicated that alternative sources of data such as the NorthStar registry (UK DMD dataset) could be consulted. However, these were not explored.”	Acknowledgement that this data could not be explored by the Company as NorthStar were unable to provide the data within the stipulated short timeframe available to respond to the ACD.	The current text suggests that the Company did not explore this potential data set as an option for time on treatment. This is factually incorrect. The Company engaged with NorthStar and submitted a data request. The Company had also included placeholders in the updated economic model so that the data could be added easily once provided. However, the Company didn’t receive the time on treatment data to inform vamorolone discontinuation due to time constraints.	Thank you for providing this clarification. The EAG has updated the text in its addendum (Point 3 - Time on treatment, Page 6). The new wording reflects the fact that the company attempted to explore the NorthStar registry and submitted a data request, but did not, however, receive the data on time for inclusion into the model.

Issue 4 No reduction in efficacy following down titration

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 6, page 21: The running of the scenario "*No reduction in efficacy or AEs following dose reduction for all treatments"* in table 6 is incorrect as it does not reflect the data. Point 4, page 6 (Final critique): The following text, *"The issue with this approach was that the ability to stand was relevant only from health states HS1 to HS3. However, it was applied across all health states which might overestimate the progression of patients with SoC treatments",* does not recognise that the data used is the best available proxy data and its exclusion would certainly	This scenario is not reflective of the published literature available (and summarized in the Company's response to the ACD), which showed a reduction in efficacy with suboptimal/reduced doses of prednisone and deflazacort. As this scenario is not clinically plausible, it should be removed. The EAG should also recognise that the data used by the Company is the best available data for HS1-3 and, the best available proxy data for HS3+ as to ensure a fair understanding of the data.	In line with the available data from FOR-DMD and clinical opinion in the Delphi panel, adverse events and efficacy for down titrated patients should be reduced. However, the EAG presents a scenario that misinforms the committee since it contradicts the published literature. Further to this, the EAG recognises the relevance of the down titrated efficacy data in *point 4, page 6* when noting it only covers health state 1 to 3 but then goes on to exclude this data for all health states. The FOR-DMD data is the best available data; to exclude it, is to contradict the literature and generate higher	The EAG does not consider this to be a matter of factual inaccuracy and retains its preference to use the original percentage efficacy reduction approach while running 'No reduction in efficacy or AEs following dose reduction for all treatments' scenario for the reasons cited in its addendum (Section 2.1, Point 4, Page 7). The EAG notes that the draft guidance following ACD (Dose reductions, 3.13) says that: "The clinical experts also stated that *they do not expect vamorolone and other corticosteroids efficacy to be different after a dose reduction*". Also, that the committee preferred assumptions (3.20) stated: "plausible assumptions after

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
lead to an underestimation of the progression of patients with SoC treatments.		uncertainty in the results presented to the Committee. The EAG also creates a false idea that the best approach is to not include down titration data for HS1-3, by suggesting that it may overestimate the down-titration impact, but fails to acknowledge that its exclusion would certainly lead to an underestimation of the impact. Failing to do so leads to a false understanding of the situation to the reader.	dose reduction when considering *no difference between vamorolone and prednisone or deflazacort".* Therefore, the consideration of this scenario as part of the EAG's preferred assumptions in its base case is in line with the committee's preferred assumptions. A scenario where dose reductions leading to reduced efficacy applied consistently to each treatment has been presented in the EAG's addendum, Table 8. this is in line with the additional analysis requested by the committee (as per section 3.20 in the draft guidance).

Issue 5 Number of carers

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Point 8 Page 12 and Point 6, Page 15 (Final critique): The EAG notes that the company has assumed 2 carers from loss of ambulation until death, this is not correct.	The EAG should recognise that the choice to increase the carers for HS3+ (non-ambulatory states) to 2 carers was based on consensus between two clinical experts' opinion gained by the Company and shared with NICE on 26th April as part of the Company's response to the draft guidance. Therefore, this is a clinically valid input, and should be maintained in the base case analysis.	The EAG has stated the Company assumed more carers for HS3+. The EAG's choice to remove the increased number of carers is not valid and is contradictory to both the clinical expert' opinion received by the Company and the testimony from the patients' representative who highlighted during the 1st Committee meeting that the entire family unit was affected when a child presents with DMD.	The EAG does not consider this to be a matter of factual inaccuracy. The company notes that they increased the number of carers in their base case from one (in their original submission) to two following clinical expert opinion, although the EAG did not receive full details of the methods or findings from the consultation. The EAG therefore cannot independently consider this evidence. Clinical opinion received by the EAG did not highlight the need for two carers for more severe health states. The EAG also notes published evidence (Landfeldt et al., 2017) that indicated that caregiver HRQoL loss involves only

			the primary caregiver, and that the inclusion of one caregiver in a model is therefore appropriate. Overall, the EAG consider that defining the appropriate number of cares to account for in the model is a methodological issue that has broader considerations beyond the number of people in a person's life that is affected by their condition. At present, including more carers in the analysis would be inconsistent with previous appraisals, raises potential inequalities across diseases and patient groups, and draws into question the appropriateness of current willingness to pay thresholds (which were defined based on the anticipated benefit of treatment to a single patient).

Issue 6 Inclusion of loss of ambulation (LOA) from fracture

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Point 8, Page 15 (Final critique): The EAG stated they were "*concerned that this modification from the original model lacked justification*" but failed to recognise the validity of the data used. Their clinical opinion, although valid, is also not consistent with wider clinical opinion as seen in the Delphi Panel conducted by the Company, and provided to NICE as reference 36 in response to the ACD. In the Delphi panel, 8/9 clinicians reached a consensus roughly in line with the Yildiz	The EAG should maintain the LOA from a fracture in their base case assumption and recognise that, in line with clinical experts' opinion, there is a significant proportion of patients who lose ambulation from a long-bone fracture.	The EAG did not acknowledge all the data available and therefore present a scenario that goes against the data from Yildiz et al, 2020 and wider clinical advice from the Delphi Panel. A consensus was reached amongst clinicians in the Delphi suggesting 20-30% lose ambulation upon having a long-bone fracture which roughly aligns with the 36.4% identified in the Yildiz 2020 paper. The inclusion of this rate is therefore justified.	The EAG does not consider this to be a matter of factual inaccuracy. The EAG's clinical experts stated that long bone fractures occur in children with DMD, whether treated or not with steroids. It was critical, therefore, that fracture outcomes were assessed over a long period in people treated with prednisone, deflazacort, or vamorolone. In VISION-DMD (where people were treated for 24 weeks) no long-bone fractures were reported in any treatment arm in the trial. Four long bone fractures were reported in the VBP15-LTE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
2020 data used in the Company's updated model.			trial but all the people in the trial were being treated with vamorolone. On the available evidence, the EAG was unable to conclude that there was any difference in long-bone fracture risk in people treated with prednisone or vamorolone 6 mg/kg. There is also uncertainty around the clinical opinion regarding the impact of LOA from non-vertebral fractures. While the company's Delphi panel reached a consensus roughly in line with Yildiz et al. 2020, clinical advice received by the EAG highlighted that loss of ambulation due to non-vertebral fractures are not common — only 2 out of 26 non ambulant boys lost ambulation following a long

			bone fracture based on their UK clinical practice experience. The EAG did consider Yildiz et al 2020 but noted the following limitations with the study: • It is a retrospective study not directly relevant to the UK population (and based on US population) and the sample size was small (n=22). • People who lost ambulation had significantly slower (pre-fracture) ten-meter walk speeds and significantly reduced ankle dorsiflexion than those who did not lose ambulation. It therefore appeared that the people with DMD who lost ambulation following the fractures were already

			progressing towards the non-ambulatory phases of the disease. The EAG notes that the LOA rate assumption interacts with the dose reduction assumptions in the way it is modelled. This interaction makes vamorolone look better in terms of loss of ambulation due to non-vertebral fractures when (as noted above) there is no evidence of a difference in fracture rates between vamorolone and prednisone or deflazacort. Finally, the EAG notes that the natural history model already includes the loss of ambulation (vertebral) due to scoliosis. The EAG is concerned that it is hard to rule out the possibility of double counting when this assumption is considered as part of the base case.

Issue 7 Increased HR for no treatment patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Point 12, page 16 (Final critique): The EAG noted "*No clear rationale for using higher HR for all health states"* was provided. The EAG is referring to the HR for no treatment patients. A rationale was provided by the Company on page 3 of the Company's response to the draft guidance which states that the 2.41 HR was applied to all health states following validation with a clinical expert in March 2024.	The EAG should recognise the company's justification and maintain the HR of 2.41 for their base case.	Currently no data is available for HS4+ for the increased 'no treatment' disease progression and proxy data based on the first 3 HS is used. The company updated the HR to the alternative proxy HR of 2.41 (from 1.41 and 1.16) to ensure a higher HR was used for 'no treatment' patients than with 'down titrated' patients (2.294). Having faster disease progression (as seen by a higher HR) for down titrated patients than with 'no treatment' patients would suggest patients are better of with 'no treatment'. This is clearly not aligned with the clinical data. Given the choice for the HR is	The EAG does not consider this to be a matter of factual inaccuracy. As the EAG did not include the HR-based approach for efficacy following dose reduction in its base case, there is no need to update the HR for 'no treatment' as the company's justification is only relevant when an HR-based approach is used. The EAG acknowledge the rationale for this assumption from the company and noted that the company response (26th April) mentioned that this is based on clinical opinion received in March 2024. However,

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		between two proxy data, the company believes that the best proxy data to use, is the data that ensures consistency with the clinical story. Therefore, the company chose to align the 'no treatment' HR with the best proxy data, a HR of 2.41. This methodology was validated by clinical experts in March 2024, whereby the expert advised that efficacy of full dose steroids compared to 'no treatments' would remain the same in all health states, and any reduction in efficacy seen in the McDonald paper is a result of patients being down-titrated.	the EAG was unclear why the clinical opinion was different in the original submission. The company's original model did not include the increased 'no treatment' disease progression. The EAG statement that the company's rationale was not clear was therefore factually accurate as the view of the EAG.

Issue 8 Spelling error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3, Page 18 (Final critique): *"Stopping rule applied for vamorolone while starting nigh-time ventilation "*	Spelling correction to night-time ventilation	Spelling error	The EAG thanks the company for identifying this typo. This has been corrected in the addendum (Section 2.3, Table 3, Page 19).

Issue 9 Irritability and aggression of behavioural issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Bullet 4, Page 10 (Addendum): *"The company did not point to any reference to 'irritability and aggression' in the study".* In further clarification provided by the Company, it was noted that the disutility was applied to several SAEs including for aggression and irritability, in TA615 and was accepted by NICE.	The EAG should recognize the reference was provided by the company and that model should maintain the 0.12 disutility in line with NICE's previous decisions.	The EAG statement suggests the company provided no clarification on this reference, this is incorrect. Further to this, the EAG's choice to halve the disutility goes against NICE's accepted decisions, and hence is a deviation from previous HTA.	The EAG does not consider this to be a matter of factual inaccuracy. Model inputs need to be justified for each submission individually, and the fact that it has been used in a previous NICE appraisal (TA615) is not a sufficient rationale. As pointed out in the addendum, the

			EAG was unable to locate any reference to ‘irritability and aggression’ within the study used and the company’s clarification response did not identify this either.

Single Technology Appraisal

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Factual accuracy check and confidential information check

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Issue 1 Muscle function outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Point 2, Page 5 (Critique of company response ACD and addendum) *"The EAG highlighted in the ACD that vamorolone was less effective than prednisone for all muscle function outcomes"*	*"The EAG highlighted in the ACD that vamorolone was numerically worse than prednisone for all muscle function outcomes"*	Stating that vamorolone was less effective in muscle function is a misinterpretation of the data, given that the VISION-DMD study was not powered for comparison with prednisone and did not constitute a non-inferiority study.	The statement made by the EAG was factually accurate and, as such, the EAG has not made any changes to the response/addendum.