National Institute for Health and Care Excellence

Health Technology Evaluation

Vamorolone for treating Duchenne muscular dystrophy [ID4024]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Santhera (company)	Vamorolone does not hold a marketing authorisation in any other indications than DMD and seems to certainly meet 3 out of 4 HST criteria: Prevalent population is lower than previously believed, 0.8 - 2.2:50,000 (Crisafulli S et al Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. Orphanet J Rare Dis. 2020 Jun 5;15(1):141. doi: 10.1186/s13023-020-01430-8), with older group of DMD men only very partially eligible for treatment. The unmet medical need for the DMD population is very high. Ataluren is only indicated for a small subset of patients who in addition are taking steroids. Vamorolone is likely to replace off-label steroid use in DMD patients irrespective of the underlying mutation. Younger patients are more likely to benefit more from treatment, but Santhera at this stage does not aim to exclude patients from treatment. Hence the patient number is likely to exceed 300.	Comment noted. Thank you. After consideration, NICE concluded that vamorolone does not meet the criteria for evaluation through the highly specialised technologies programme. This appraisal has been scheduled into the single technology appraisal work programme.

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		DMD as a very rare condition significantly shortens life and severely impairs its quality. Criterion 4 is certainly met hence there are no other satisfactory treatment options, and vamorolone is likely to offer significant additional benefit over existing treatment options. The off-label use of steroids is associated with treatment-related side effects to an extend that treatment is often discontinued or dosing is reduced to sub-optimal levels. The recent FOR-DMD study illustrates how these side-effects are dose-dependent and may lead to dose-reductions or discontinuation. (Guglieri at al 2022, Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular Dystrophy. JAMA. 2022;327(15):1456-1468. doi:10.1001/jama.2022.43). Vamorolone offers similar efficacy compared to steroids combined with a much favourable safety profile leading to better compliance and more patients benefitting for longer from an anti-inflammatory treatment. E.g. Out of 164 pts, 153 (93%) are still on vamorolone therapy during the long-term follow-up. Ataluren is indicated for a very small DMD subpopulation and patients on ataluren are in addition treated with steroids. For the above reasons we regard vamorolone as a border line case and suggest vamorolone could be assessed in line with other related NICE recommendations (cf appendix B) under the NICE highly specialised technologies guidance.	
	The John Walton Muscular Dystrophy Research Centre, Newcastle	DMD is a rare disease affecting children and associated with progressive, severe disability. There are limitations in the evidence base available on the natural history of the disease which would be more appropriately considered and evaluated by the highly specialised technology appraisal.	Comment noted. Thank you. After consideration, NICE concluded that vamorolone does not meet the criteria for evaluation through the

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		The highly specialised technology appraisal would therefore be more appropriate for this evaluation to reflect the complex nature of rare diseases. Moreover HST has already developed expertise in the assessment of new technologies for DMD	highly specialised technologies programme. This appraisal has been scheduled into the single technology appraisal work programme.
	Action Duchenne, Duchenne UK & MD UK	This treatment has been assigned to go through the Single Technology Appraisal Route. We feel that it is imperative it is reassigned to the Highly Specialised Technology Route (HST). Duchenne Muscular Dystrophy (DMD) is a rare disease, with approximately 2500 people in the UK affected by the condition. While routing criteria 1 and 2 may exclude Vamorolone from HST, NICE is explicitly allowed flexibility in both criteria. Not all those 2500 people will be eligible for treatment with Vamorolone. We urge NICE to review how many individuals this would entail to determine whether HST would be a more appropriate route given the uncertainty and issues around cost effectiveness that often accompany a rare disease appraisal. If this isn't possible, we would still appreciate having further clarity on what flexibilities will be exercised to ensure Vamorolone is fairly assessed. It is imperative that the routing of the appraisal does not pre-determine its outcome.	Comment noted. Thank you. After consideration, NICE concluded that vamorolone does not meet the criteria for evaluation through the highly specialised technologies programme. This appraisal has been scheduled into the single technology appraisal work programme.
	Genetic Alliance	Genetic Alliance UK would encourage that this technology be assessed via the HST route rather than STA. Duchenne Muscular Dystrophy (DMD) is a rare condition and we have been informed by Muscular Dystrophy UK that	Comment noted. Thank you. After consideration, NICE concluded that vamorolone does not

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		this technology would only be applicable to individuals on corticosteroids, therefore the eligible population is smaller than what is stated.	meet the criteria for evaluation through the highly specialised technologies programme. This appraisal has been scheduled into the single technology appraisal work programme.
Wording	Santhera (company)	DMD is an X-chromosome linked disease almost exclusively affecting males. DMD is a chronic, debilitating disease in which HRQoL continuously decreases. A recent paper (Powell et al. Measuring quality of life in Duchenne muscular dystrophy: a systematic review of the content and structural validity of commonly used instruments. Health Qual Life Outcomes. 2020 Aug 3;18(1):263. doi: 10.1186/s12955-020-01511-z) shows that most if not all of the used PRO tools used in DMD are doubtful or inadequate. “Ataluren has a NICE recommendation within a managed access agreement and is subject to NICE review in a subset of DMD patients, Ataluren aims to treat the underlying cause of disease rather than alleviating symptoms. It does not reduce the need for steroids as boys still need to continue steroid treatment and is therefore unlikely to be a relevant comparator.”	Comment noted. Thank you. Ataluren is recommended for treating DMD and is therefore identified in the scope background section as a related health technology evaluation.
	John Walton MD Research Centre	The remit does not fully consider the complexity of DMD and its treatments. Corticosteroids are part of the care recommendations for DMD however it is important to notice that they are not licensed for DMD in UK/EU. While it is expected the new technology to be similar in efficacy to standards of care, including corticosteroids, it is suggested to have different side effect profile which can have a significant impact on disease management, use of	Comment noted. Thank you for clarifying these points. The scope aims to provide a broad overview of the condition. The committee will appraise

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		resources and quality of life. This is not fully captured in the remit and should be part of the cost effectiveness evaluation. Several components of the management of DMD, in term of required monitoring and treatments, are in fact related to the management of steroid related adverse events, in addition to disease complications. DMD is a rare disease, resulting in gaps in outcome measure training implementation and interpretation nationally. Outcome measures might therefore not be always available or can be complex in their interpretation (e.g. frequency of falls can suggest worsening of the disease but in children could also suggest an increase in physical activity). There is a lack of evidence of the natural history of DMD in older patients which can impact consideration of late-disease complications (e.g. scoliosis and upper body movement). QoL measures for DMD are emerging but data are very limited. Being a severe, chronic and fatal disease affecting children, the impact of a diagnosis as well as the disease on the family should also be considered	vamorolone within its marketing authorisation and review the clinical and economic evidence presented.
	Action Duchenne, Duchenne UK & MD UK	The wording is appropriate.	Comment noted. Thank you.
Additional comments on the draft remit	Santhera (company)	The unmet medical need for the DMD population is very high. Ataluren is only indicated for a small subset of patients who in addition are taking steroids. Due to the favourable safety profile, vamorolone is likely to replace off-label steroid use in DMD patients irrespective of the underlying mutation. Corticosteroid side-effects kick in at the moment of therapy start, including behavioural changes, height growth impairment, endocrinological changes and bone demineralisation, leading to fractures. Prevention and/or reduction	Comment noted. Thank you for clarifying these points.

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		of these side-effects can be achieved by replacing corticosteroids with vamorolone. For the above-mentioned side effects, steroid use in DMD patients is very heterogenous. Some patients and their carers refuse the treatment at all and sometimes an intermittent treatment scheme is applied to cope with side effects. However, the FOR-DMD study found that on-off treatment schemes result in reduced efficacy. Vamorolone is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients [redacted]	
	John Walton MD Research Centre	DMD remains a disease with high unmet needs therefore the evaluation should be considered as urgent. Although corticosteroids are part of the care recommendations, there is no licensed treatment in the UK available to all patients with DMD	Comment noted. Thank you.
	Action Duchenne, Duchenne UK & MD UK	There is an urgency to this evaluation, to ensure that Valmorolone can be accessed by patients as soon as possible given the severe side effects associated with corticosteroids but yet are heavily relied on given they stabilise or even improve muscle strength for a period of time.	Comment noted. Thank you.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Santhera (company)	We suggest several changes/additions.	Thank you. These have been addressed below.

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	John Walton MD Research Centre	The following points should be included in the background: - DMD is characterised by progressive muscle weakness and wasting affecting all body muscles. Symptoms usually present between the age of 2-3 years with delayed motor/global development, difficulties in walking, running and jumping. With the progression of muscle weakness, affected children develop difficulties climbing stairs, getting up from the floor and climbing stairs. This is followed by involvement of the upper limb muscles, causing difficulties in lifting their arm and reach hand to mouth. Without interventions, children with DMD lose the ability to walk before the age of 10 years. Weakness in the trunk muscles can lead to scoliosis. Muscle weakness in the upper limbs lead to inability to move the arms or limited movements in the distal muscles only (fingers). The disease also affects the respiratory and cardiac muscles. Respiratory involvement usually manifests after the age of loss of ambulation and requires treatment with ventilatory support, initially at night only but full time ventilatory support is often required in older patients. Cardiomyopathy can present at any age although it is more frequent after the age of 10 years. - Learning difficulties and behavioural problems are common in DMD and range from mild impairment of short-term memory to severe autistic spectrum disorder - Current standards of care, including corticosteroids can improve muscle strength and function over a certain period of time. Corticosteroids have been reported to prolong the ability to walk independently (with a mean age of loss of ambulation around 13-14 years), preserve upper limb function, delay respiratory complication and development of heart involvement and postpone or reduce the requirement of orthopedic interventions such as scoliosis.	Comment noted. Thank you. The background section of the scope aims to provide a broad overview of the condition.

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		- Corticosteroids are the only treatment currently available for all patients with DMD and are part of the care recommendations. Corticosteroids are however associated with several side effects which impact management and quality of life. These include excessive weight gain, growth restriction, cushingoid appearance, bone fragility with increase risk of vertebral and long bone fractures, delayed puberty, exacerbation of behavioural problems, adrenal suppression, gastro-intestinal issues (ulcers), hypertension and increased risk of cataracts.	
	Action Duchenne, Duchenne UK & MD UK	There are a few areas of modification and addition to the background information we would like to see: 1) "Initial symptoms of DMD usually present between the ages of 1 and 3 years": there are symptoms of DMD from birth, but they usually only present to caregivers in subsequent years. DMD can be diagnosed at birth by newborn screening. 2) "After the age of 12 most children will need to use a wheelchair as their muscles weaken and they lose the ability to walk.": Patients may become entirely dependent by the age of 12, most boys use wheelchairs at 6-7 years of age. 3) "and physical aids (such as wheelchairs, leg braces or crutches)": we are not aware of the use of crutches by patients with DMD, they would be too heavy to use. 4) the treatments and support described are not available to all patients due to how care is managed differently across the UK. The difference in care management across the UK leads to different health outcomes for patients and their families. 5) We would like more expansion on the "associated… side effects" of steroids in order to provide some context for Vamorolone in regard to	Comment noted. Thank you. The background section of the scope aims to provide a broad overview of the condition.

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		a chronic, progressive condition with different trajectories of decline. Specific mention of the FOR-DMD trial is encouraged.	
Population	Santhera (company)	The total DMD population seems to be overestimated by approximately 25%, based on the most recent literature. Based on the most recent literature, the incidence of DMD is 1 in 5,050 male live births (CI: 1 in 4,237 – 6,024 (Crisafulli 2020). Based on a birth rate of approximately 310,000 boys annually (www.ons.gov.uk) and based on current DMD life expectancies (Broomfield 2021) the total number of DMD patients (aged 0 – 40 years) in the UK should lie between 1,800 – 1,900.	Comment noted. Thank you for providing this. The incidence estimates included in the scope are based on those reported. Please see references.
	John Walton MD Research Centre	Yes.	Comment noted. Thank you.
	Action Duchenne, Duchenne UK & MD UK	Yes	Comment noted. Thank you.
Subgroups	Santhera (company)	Vamorolone is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients [redacted] Younger DMD boys are expected to benefit more, with less behavioural problems, by prevention of negative effects on bone metabolism, with reduced fracture rates, and no height growth impairment when treated with vamorolone. In the older population, similar efficacy to steroids - cardioprotective and respiratory muscle protective effects - can be expected, still with less side-effects	Comment noted. Thank you.

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	John Walton MD Research Centre	No. The current clinical trial data on vamorolone are limited to young children with DMD. However anti-inflammatory drugs (corticosteroids) are currently recommended to all patients with DMD and should not be discontinued at loss of ambulation or adulthood unless of severe side effects. Moreover, based on pre-clinical evidences vamorolone might have a beneficial impact on cardiac function and therefore could benefit all patients with DMD a different ages and disease status	Comment noted. Thank you. The population has been written to be inclusive. The technology will be evaluated in line with its marketing authorisation.
	Action Duchenne, Duchenne UK & MD UK	The population (people with DMD) are defined appropriately.	Comment noted. Thank you.
Comparators	Santhera (company)	Yes, all have been included	Comment noted. Thank you.
	John Walton MD Research Centre	The comparator (standards of care including corticosteroids) is appropriate however it should be noted that corticosteroids are not licensed for DMD in the UK/EU. Ataluren is not a valid comparator to the new technology. Ataluren is only available for a small sub-population of DMD and is prescribed in combination to corticosteroids. Age of onset of treatment should be considered an important factor when including comparators in young children. Other factors might need to be considered for other sub-populations.	Comment noted. Thank you. Ataluren has been included in the background section of the scope only as a related health technology evaluation.
	Action Duchenne,	The current standard of care with corticosteroids is an appropriate comparator.	Comment noted. Thank you. Ataluren has been

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	Duchenne UK & MD UK	The scope includes mention of ataluren. We have two concerns regarding this; 1. It is currently available only through a Managed Access Agreement, meaning that it hasn't yet been fully recommended for use on the NHS, and; 2. Ataluren is used in conjunction with steroids and we would anticipate that it would also be used in conjunction with Vamolorone, should it be recommended for use by NICE. It is therefore not strictly a comparator. 3. Additionally, ataluren's mechanism of action does not seek to directly address inflammation and it is only suitable for those patients with a nonsense mutation (which is approximately 10% of the Duchenne MD population).	included in the background section of the scope only as a related health technology evaluation.
Outcomes	Santhera (company)	Suggested outcome measures: • walking ability (ambulation) • muscle function • height growth • bone metabolism • bone fractures • endocrine function • ability to undertake activities of daily living • adverse effects of treatment	Comment noted. Thank you. The final scope has been updated to include additional outcomes.
	John Walton MD Research Centre	Outcomes should reflect the clinical outcomes collected as part of the completed clinical trials with vamorolone (e.g. NSAA, time to loss of ability to rise from floor, time to loss of ability to walk). Outside clinical trial data, upper limb function (e.g. ability to reach hand to mouth) is relevant and clinically meaningful and should be measured using the PUL 2.0.	Comment noted. Thank you. The final scope has been updated to include additional outcomes.

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		Time to independent transfer is a really important outcome for patients and families, affecting independency however there are limited data on the natural history of this outcome Frequency of falls can be very difficult to monitor/record (especially in children attending nursery/school/play groups where falls might not be monitored and the young child might not accurately report them) and it can reflect different factors (it can indicate worsening of the disease but also increase in physical activity; falls tends to be less frequent in older patients as they become more conscious or wheelchair dependent) Adverse events will be important outcomes as they might be the major difference between the comparator and the new technology (e.g. fractures, height restriction, weight gain, delayed puberty, behavioural problems, etc) and the associated impact on QOL	
	Action Duchenne, Duchenne UK & MD UK	Yes, ensuring that the mental health aspects within the health-related quality of life (for patients and carers) outcomes are explicitly reviewed. Additionally, it is essential to include a quantitative evaluation of carer utility values in relation to Quality of Life benefits. Also, we would widen this to include upper-body function to ensure the focus is on both the ambulant and non-ambulant populations.	Comment noted. Thank you. The final scope has been updated to include additional outcomes.
Equality	Santhera (company)	In general, vamorolone is only indicated in boys with DMD, as no toxicology studies in females have been performed. Apart from that, the number of girls living with DMD is estimated to be less than 10 in the UK. Otherwise not applicable.	Comment noted. Thank you. The committee will consider any relevant equality issues when it makes its recommendations.

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	John Walton MD Research Centre	DMD is an X-linked disease and therefore mainly affects boys. Corticosteroids are not routinely used or recommended in female carriers, even if symptomatic.	Thank you. The committee will consider any relevant equality issues when it makes its recommendations.
	Action Duchenne, Duchenne UK & MD UK	It is important to ensure that no patient has to travel excessive distances to receive the treatment given the level of disability that many will face.	Thank you. The committee will consider any relevant equality issues when it makes its recommendations.
Other considerations	Santhera (company)	Measuring QoL has proven to be particularly challenging in DMD and is a controversial topic (Powell et al 2020). This should be considered during the process.	Comment noted. Thank you. The committee will consider the impact upon quality of life during the technology evaluation process.
	John Walton MD Research Centre	The new technology is suggested to have similar efficacy to current treatment but better side effect profile. How is this captured in the current remit/scope draft?	Comment note. Thank you. The committee will appraise vamorolone within its marketing authorisation and review any clinical and economic evidence presented.
	Action Duchenne,	None provided.	Thank you.

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	Duchenne UK & MD UK		
Questions for consultation	Santhera (company)	Where do you consider vamorolone will fit into the existing care pathway for DMD? Prednisone 0.75 mg/kg/day is the current standard-of-care. Vamorolone is equally effective as prednisone. Vamorolone has significantly fewer and less severe side-effects and unlike steroids (prednisone or deflazacort) does not negatively affect bone-metabolism or growth. Vamorolone could replace prednisone as standard-of-care in the treatment of DMD boys [redacted] and become the backbone therapy for people with DMD Which treatments are considered to be established clinical practice in the NHS for Duchenne muscular dystrophy? Prednisone 0.75 mg/kg/day. Is ataluren a relevant comparator in the treatment of inflammation associated with DMD? No, as it is mutation specific and only addresses a small subgroup (10-15%) of DMD patients. Ataluren patients are also taking steroids. Vamorolone is expected to replace these. Should reduction in standard corticosteroid use be included as an outcome? Yes, as vamorolone could make standard corticosteroids obsolete. Due to its more benign side-effect profile, vamorolone is better tolerated and will improve compliance. To illustrate: 153/164 (93%) vamorolone study-patients are currently in long-term follow-up. Would vamorolone be a candidate for managed access? Unclear at present, potentially.	Comment noted. Thank you for providing these responses. The committee can consider these during the evaluation process.

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		Do you consider that the use of vamorolone can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. DMD is a chronic, debilitating disease in which HRQoL continuously decreases. A recent paper (Powell et al. 2020) states that most if not all of the used PRO tools used in DMD are doubtful or inadequate. Steroid treatment is associated with severe side effects that additionally impair patients HRQoL to an extend that dosing has to be reduced to sub-optimal levels or treatment has to be discontinued. 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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which vamorolone will be licensed; n.a. • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; n.a. • could have any adverse impact on people with a particular disability or disabilities. n.a. Would it be appropriate to use the cost-comparison methodology for this topic? No	

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		Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? No, vamorolone offers better compliance and is safer, with fewer and less severe side-effects. Resource use is expected to increase due to higher drug cost, partially to be set off with health state cost and hospitalisations for fractures and other side-effects. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes. Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? The FOR-DMD trial found that deflazacort and prednisone are equally effective when taking daily while on-off treatment schemes do not yield the expected efficacy.	
	John Walton MD Research Centre	None provided.	Noted. Thank you.
	Action Duchenne, Duchenne UK & MD UK	None provided.	Noted. Thank you.
	Santhera (company)	None provided.	Noted. Thank you.

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Additional comments on the draft scope	John Walton MD Research Centre	None provided.	Noted. Thank you.
	Action Duchenne, Duchenne UK & MD UK	Plans to ensure that patients can transition from the current standard of care to the new treatment, if approved, should be addressed. Further, if the side effects are fewer and the efficacy greater than the current standard of care, then this would be a step change for this population. We recommend that the following questions are also addressed: Do you consider that the use of Vamorolone can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Do you consider that there will be any barriers to adoption of this technology into practice?	Comment note. Thank you. Any additional benefits which are not captured by the QALY and barriers to adoption of the technology may be considered by the committee when it makes its recommendations.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Neonatal and Paediatric Pharmacists Group