

HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

Vamorolone for treating Duchenne muscular dystrophy

NIHRIO ID	12919	NICE ID	10613
Developer/Company	Santhera UK LTD	UKPS ID	Not Available

Licensing and market availability plans	Currently in phase II clinical development.
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SUMMARY

Vamorolone is currently in clinical development for the treatment of boys with Duchenne muscular dystrophy (DMD). DMD is a rare genetic, muscle wasting disease caused by a change (mutation) in the X chromosome that results in loss of the production of a protein called dystrophin. The disease primarily affects boys with symptoms including difficulty walking beginning to develop from the age of 3. As the disease progresses, muscle wastage becomes more severe resulting in increased levels of disability and serious, life threatening complications such as disease of the heart muscle and breathing difficulties. There is an unmet need as current treatments involving high-dose steroids have significant side effects that affect the patient's quality of life.

Vamorolone is a new type of oral anti-inflammatory medicinal product that works by blocking a pathway known as NFkB, which is known to be associated with DMD symptoms. Vamorolone is designed to work in a different way to steroids resulting in the same treatment efficacy but with fewer side effects compared to steroids. If licenced, vamorolone will offer an additional treatment option for male paediatric patients with DMD aged 4 years and older.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

PROPOSED INDICATION

Treatment of male patients aged 4 years and older DMD.¹

TECHNOLOGY

DESCRIPTION

Vamorolone (VBP15) is a first-in-class anti-inflammatory medicinal product that shows potent inhibition of pro-inflammatory NFκB pathways (one of the earliest molecular pathologies of dystrophin-deficient muscle in DMD patient) via high-affinity binding to the glucocorticoid receptor, high affinity antagonism for the mineralocorticoid receptor, and membrane stabilisation properties.^{2,3} It differs from other corticosteroids by lacking an 11-carbon oxygen group (hydroxy or carbonyl) that is 1 of 5 molecular contact sites with the glucocorticoid receptor and is a potent antagonist of the mineralocorticoid receptor. The differential mechanism of action of vamorolone compared with traditional corticosteroid anti-inflammatory drugs is attributed to the loss of gene transcriptional activities associated with glucocorticoid response element binding and activation, potent antagonist activity for the mineralocorticoid receptor, superior membrane stabilisation properties and retention of the distinct NFκB inhibitory (anti-inflammatory) activities.³

Vamorolone is currently in clinical development for the treatment of males aged 4 years and older affected with DMD. In the pivotal phase IIb clinical trial (NCT03439670), participants receive vamorolone 2.0 mg/kg/day or 6.0 mg/kg/day by oral administration for 24 weeks.¹

INNOVATION AND/OR ADVANTAGES

Current management of DMD includes treatment with corticosteroids to delay loss in walking ability; however, they are associated with significant adverse events.⁴ Vamorolone binds to the same receptors as corticosteroids and retains the associated anti-inflammatory activities.^{3,5} However, vamorolone modifies the downstream activity of receptors and therefore has the potential to dissociate efficacy from the safety concerns of typical steroid medications for DMD.⁵

Preclinical studies suggest that vamorolone has the potential to increase the therapeutic window, slow disease progression, and improve quality of life and lifespan for all DMD patients.^{2,6}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Vamorolone does not currently have Marketing Authorisation in the EU/UK for any indication.

Vamorolone has the following regulatory designations:⁷

- Granted orphan drug status by the EMA in 2019 for the treatment of DMD
- Granted a Promising Innovative Medicine (PIM) status by the MHRA for the treatment of DMD in October 2019.

Vamorolone is not currently in phase II or III development for any other indications.⁸

PATIENT GROUP

DISEASE BACKGROUND

The muscular dystrophies are a group of inherited genetic conditions caused by changes (mutations) in the genes responsible for the structure and functioning of a person's muscles. These mutations result in changes in the muscle fibres that interfere with the muscles' ability to function.⁹ There are around 30 different types of muscular dystrophies, the most common and severe form of which is DMD, which is caused by a mutation of the DMD gene on the X chromosome that results in a complete lack of the production of the protein dystrophin. Dystrophin transfers the force of muscle contraction from the inside of the muscle cell outward to the cell membrane.^{10,11} DMD is inherited as an X-linked disease and therefore predominantly manifests in males, as females have a second X chromosome that can compensate for a mutation in the first X chromosome.^{10,12} Most DMD cases are inherited, although occasionally the disease may develop as a result of spontaneous mutation of the dystrophin gene (de-novo or sporadic cases).¹⁰

The clinical hallmarks of DMD include progressive weakness and wasting (atrophy) of various muscles of the body.^{10,11} Muscle weakness, the primary symptom of DMD, usually occurs in boys between the ages of 2 and 3 affecting the ability of patients to run, jump and walk. Weakness firstly occurs in the proximal muscles, then the distal limb muscles and often lower external muscles are affected before the upper external muscles.¹³ Progressive muscular damage and degeneration occurs in people with DMD, resulting in muscular weakness, associated motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy.¹⁴ Most patients lose the ability to walk by the age of 12 and require ventilatory support by 25 years of age.¹⁵

DMD is also associated with a substantial cost burden to society and affected families and significantly impairs quality of life in both patients and caregivers.¹⁶

CLINICAL NEED AND BURDEN OF DISEASE

DMD is the most common fatal genetic disease diagnosed in childhood.¹² The prevalence is estimated to be 19.5 cases per 100,000 live male births in the UK and it is estimated that there are currently around 2,500 boys and young men living in the UK with DMD.^{14,17} The average lifespan of a patient with DMD is 29 years.¹⁸

In England (2019/20), there were 2,251 hospital admissions for muscular dystrophy (ICD-10 G71.0, which includes DMD), resulting in 2,369 finished consultant episodes and 3,441 bed days.¹⁹

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Currently there is no cure for DMD but treatments and therapies aim to ease the symptoms and amongst the ambulant patient population (those who are able to walk), increasing the time a patient is able to walk is one of the major aims of treatment.^{18,20} Steroids are often prescribed to slow progression of muscle weakness, reduce the development of scoliosis and delay the onset of breathing and heart problems.²⁰ Physiotherapy and orthotics (splints) are also used to help delay contractures and maintain mobility.¹⁷

CURRENT TREATMENT OPTIONS

NICE currently recommends ataluren for treating DMD resulting from a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk.²¹

Two commonly prescribed steroids to treat children with DMD are prednisolone 0.75mg/kg/day and deflazacort 0.9mg/kg/day.²²

PLACE OF TECHNOLOGY

If licenced, vamorolone would offer an additional treatment option to ambulant male DMD patients aged 4 years and older, for whom few treatment options available and most of these are associated with significant adverse effects.^{1,3,21}

CLINICAL TRIAL INFORMATION

Trial	VBP15-004, NCT03439670 ; A phase IIb randomised, double-blind, parallel group, placebo and active controlled study with double-blind extension to assess the efficacy and safety of vamorolone in ambulant boys with Duchenne muscular dystrophy (DMD) Phase II – Completed Locations: 6 EU countries, UK, USA, Canada and other countries Study completion date: August 2021
Trial design	Randomised, double-blind, parallel group, placebo- and active-controlled
Population	N=121; males aged 4 to 7 years; ambulant subjects with DMD (centrally confirmed diagnosis of DMD (confirmed by TRINDS central genetic counsellor); able to walk independently without assistive devices; able to complete the time to stand test (TTSTAND) without assistance in <10 seconds
Intervention(s)	<ul style="list-style-type: none"> • Vamorolone (oral administration) <ul style="list-style-type: none"> - 2.0mg/kg/day - 6.0mg/kg/day
Comparator(s)	<ul style="list-style-type: none"> • 0.75 mg/kg/day prednisone (oral administration) • Vamorolone (oral administration) <ul style="list-style-type: none"> - 2.0mg/kg/day - 6.0mg/kg/day • Placebo (oral administration)
Outcome(s)	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> • Efficacy of vamorolone at 6.0mg/kg/day vs placebo group as measured by change from baseline of TTSTAND velocity [Time frame: 24 weeks] <p>See trial record for full list of outcome measures</p>
Results (efficacy)	-

Results (safety)	-
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Trial	VBP15-002, NCT02760264 ; A Phase IIa open-label, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys with Duchenne Muscular Dystrophy (DMD) Phase II - Completed Locations: 1 EU country, UK, USA, Canada and other countries Primary completion date: May 2018
Trial design	Open-label, sequential assignment, multiple ascending dose
Population	N=48; males aged 4 to 7 years old (inclusive); confirmed diagnosis of DMD (confirmed by central genetic counsellor); able to complete the TTSTAND without assistance
Intervention(s)	Vamorolone (oral administration) <ul style="list-style-type: none"> - 0.25mg/kg/day - 0.75mg/kg/day - 2.0mg/kg/day - 6.0mg/kg/day
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: <ul style="list-style-type: none"> • Number of participants with treatment-emergent adverse events (TEAEs) as assessed by CTCAE version 4.03 [Time frame: up to 30 days after final drug administration] <p>See trial record for full list of outcome measures</p>
Results (efficacy)	Exploratory biomarkers of pharmacodynamic efficacy showed an anti-inflammatory mechanism of action and a beneficial effect on plasma membrane stability, as demonstrated by a dose-responsive decrease in serum creatine kinase activity. ²³
Results (safety)	Vamorolone was safe and well-tolerated through the highest dose tested (6.0mg/kg/day) and pharmacokinetics of vamorolone were similar to prednisolone. Using pharmacodynamic biomarkers, the study demonstrated improved safety of vamorolone versus glucocorticoids as shown by reduction of insulin resistance, beneficial changes in bone turnover (loss of increased bone resorption and decreased bone formation only at the highest dose level), and a reduction in adrenal suppression. ²³

Trial	VBP15-003, NCT02760277 ; A Phase II open-label, multicentre, long-term extension study to assess the long-term safety and efficacy of vamorolone in boys with Duchenne Muscular Dystrophy (DMD) Phase II - Completed Locations: 1 EU country, UK, USA, Canada and other countries Primary completion date: April 2018
Trial design	Open-label, sequential assignment, multicentre, long-term extension

Population	N=48; males aged 4 to 7 years; Subjects who previously completed study VBP15-002 up to and including the week 4 follow-up assessments within 8 weeks prior to enrolment
Intervention(s)	Vamorolone (oral administration) <ul style="list-style-type: none"> - 0.25mg/kg/day - 0.75mg/kg/day - 2.0mg/kg/day - 6.0mg/kg/day
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: <ul style="list-style-type: none"> • Number of participants with TEAEs as assessed by CTCAE version 4.03 [Time frame: 24 weeks] <p>See trial record for full list of outcome measures</p>
Results (efficacy)	Mean changes from baseline to weeks 12 and 24 for the primary efficacy outcome, time to stand from supine measured as velocity, showed dose- and time-related improvements. The mean difference in change from baseline to week 24 was significant for the comparison of the 2.0 and 6.0 mg/kg/day groups to the lowest 0.25 mg/kg/day group (p=0.02 and p=0.04, respectively). The mean difference in change from baseline to week 24 was also significant for comparison of the 2.0 mg/kg/day vamorolone group to an untreated comparator cohort (p=0.04). ²⁴
Results (safety)	Oral administration of vamorolone at all doses tested (0.25, 0.75, 2.0 and 6.0 mg/kg/day in 12 boys per treatment group) was safe and well tolerated. Vamorolone treatment led to increased serum levels of osteocalcin, a biomarker of bone formation, suggesting possible reduction of bone morbidities typically associated with corticosteroids. Biomarker outcomes for adrenal suppression and insulin resistance also indicated better tolerability of vamorolone treatment, relative to published studies of corticosteroid therapy. ²⁴

Trial	VBP15-LTE, NCT03038399 ; A 24-month Phase II open-label, multicentre, long-term extension study to assess the long-term safety and efficacy of vamorolone in boys with Duchenne Muscular Dystrophy (DMD) Phase II - Completed Locations: 1 EU country, UK, USA, Canada and other countries Primary completion date: April 2020
Trial design	Open-label, parallel assignment, multicentre, long-term extension
Population	N=46; males aged 4 to 7 years; Subjects who previously completed study VBP15-003 up to and including the week 24 final assessments
Intervention(s)	Vamorolone (oral administration) <ul style="list-style-type: none"> - 0.25mg/kg/day - 0.75mg/kg/day - 2.0mg/kg/day - 6.0mg/kg/day

Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: <ul style="list-style-type: none"> Number of participants with TEAEs as assessed by CTCAE version 4.03 [Time frame: 24 months] See trial record for full list of outcome measures
Results (efficacy)	DMD trial participants treated with either 2.0 or 6.0mg/kg/day of vamorolone for the full 18 month period (n=23) showed clinical improvement of all motor outcomes from baseline to month 18. ³
Results (safety)	Physician-reported incidences of adverse events (AEs) for Cushingoid appearance, hirsutism, weight gain, and behaviour change were less for vamorolone than published incidences for prednisone and deflazacort. ³

ESTIMATED COST

The estimated cost of vamorolone is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE highly specialised technology guidance. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (Review of HST3). (GID-HST10044). Expected date of issue to be confirmed.
- NICE highly specialised technology guidance. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (HST3). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS Standard Contract (2013/2014). For Diagnostic Service for Rare Neuromuscular Disorders (all ages). D04/S(HSS)/a

OTHER GUIDANCE

- NHS Scotland. Paediatric guidance for management of DMD in Scotland. 2012.²⁵

ADDITIONAL INFORMATION

Santhera UK LTD did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK

PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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