# A Phase IIb Randomized, 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)

Published: 25-02-2019
Last updated: 09-04-2024

Primary objectives: 1. To compare the efficacy of vamorolone administered orally at daily doses of 6.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Musculoskeletal and connective tissue disorders congenital |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON50318

**Source**
ToetsingOnline

**Brief title**
VBP15-004 - VISION DMD

### Condition

- Musculoskeletal and connective tissue disorders congenital
- Muscle disorders

**Synonym**
Duchenne Muscular Dystrophy; Muscular Disorder

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** ReveraGen BioPharma, Inc.
**Source(s) of monetary or material Support:** REVERAGEN en horizon2020

## Intervention

**Keyword:** ambulant boys ages  4 to < 7 years, Duchenne Muscular Dystrophy, Vamorolone

## Outcome measures

### Primary outcome

Tolerability:

1. Premature discontinuations of study treatment due to adverse events.

Efficacy:

1. Time to Stand Test (TTSTAND) velocity (rise/second): Comparison of the vamorolone 6.0 mg/kg/day dose level group versus the placebo group in change from baseline to the Week 24 assessment.

### Secondary outcome

Safety:

1. BMI z-score: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.

2. Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by system organ class (SOC): Overall by treatment, by treatment and relationship, and by treatment and intensity (see Section 7.5);

3. Vital signs (sitting blood pressure, heart rate, respiratory rate, and body temperature): Change from baseline to each of the scheduled on-treatment and

post-treatment assessment time points;

4. Body weight and height: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points;

5. Cushingoid features: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points (changes from baseline will be recorded as AEs);

6. Clinical laboratory values: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points in:

* Hematology and clinical chemistry
* Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL])
* Vitamin D level
* Urinalysis;

7. 12-lead electrocardiogram (ECG): Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points;

8. 2D-echocardiogram: Change from baseline to Week 24 and Week 48;

9. Dual-energy x-ray absorptiometry (DXA) scan: Change from baseline to Week 24 and Week 48 in spine BMD, total body BMD, spine and total body bone mass, and total body composition (lean mass, fat mass, fat-free mass, Lean Mass Index, and Fat Mass Index);

10. Spine x-rays: Change from baseline to Week 24 assessment;

11. Eye examination for detection of clinically significant abnormalities (cataracts and/or glaucoma) at Week 24 and Week 48 assessments compared to baseline;

12. ACTH test: measure of adrenal suppression at Week 24 and Week 48.

Percentage of subjects in each treatment group with cortisol levels <18 *g/dL

(or 500 nM) 30 or 60 minutes after stimulation with Cosyntropin.

13. Linear growth velocity: Change from baseline to each of the scheduled

on-treatment and post-treatment assessment time points in height percentile for

age

Efficacy:

1.Change from baseline to Week 24 for the following comparisons:

-TTSTAND velocity, vamorolone 2.0 mg/kg/day vs placebo

- 6 Minute Walk Test (6MWT) meters walked, vamorolone 6.0 mg/kg/day vs. placebo

- 6 Minute Walk Test (6MWT) meters walked, vamorolone 2.0 mg/kg/day vs. placebo

- Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 6.0 mg/kg/day vs.

placebo

- Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 2.0 mg/kg/day vs.

placebo

- 6MWT meters walked, vamorolone 6.0 mg/kg/day vs. prednisone

- 6MWT meters walked, vamorolone 2.0 mg/kg/day vs. prednisone

2. Change from baseline to each of the scheduled study assessment time points

for each treatment group up to Week 48 for:

- TTSTAND

- TTCLIMB

- TTRW

- 6MWT

- NSAA

- Hand-held myometry

- ROM

For other study parameters see protocol section 2.2 Study Endpoints.

# Study description

**Background summary**

The purpose of this study is to see if vamorolone is effective (improves or stabilizes muscle strength and function) and has fewer side effects than corticosteroids in children with DMD.

Boys with Duchenne muscular dystrophy (DMD) experience progressive muscle weakness as they grow up. Corticosteroids such as prednisone (or prednisolone) and deflazacort are currently the only class of medication available for all boys with DMD that has been shown to prolong walking ability over a certain period of time. However, corticosteroids are associated with several side effects (undesirable effects of the drug), including weight gain, behavioural problems, growth restriction, increased risk of bone fractures. Undesirable side effects are the main reason why corticosteroids are not always prescribed or are discontinued even though they have been proven to have a positive effect on muscle function and delay the development of some complications in DMD.

**Study objective**

Primary objectives:
1. To compare the efficacy of vamorolone administered orally at daily doses of 6.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD; and
2. To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years with DMD.

Secondary objectives:
1. To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD;
2. To compare the safety of vamorolone administered orally at daily doses of

2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD;
3. To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD;
4. To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 48-week treatment period in ambulant boys ages 4 to <7 years with DMD vs. untreated DMD historical controls;
5. To compare the safety of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 48-week treatment period in ambulant boys ages 4 to <7 years with DMD vs. prednisone-treated DMD historical controls; and
6. To evaluate the population pharmacokinetics (PK) of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years with DMD.

Exploratory objectives:
1. To evaluate the satisfaction with treatment of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD;
2. To evaluate the effect of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg on Quality of Life and neuropsychology;
3. To assess the ease of administration of the study medication suspension to ambulant boys ages 4 to <7 years with DMD;
4. To compare the effects of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. placebo on potential serum pharmacodynamics (PD) biomarkers of safety and efficacy in ambulant boys ages 4 to <7 years with DMD; and
5. To compare the effects of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg on potential serum PD biomarkers of safety and efficacy in ambulant boys ages 4 to <7 years with DMD.
6. To compare the effects of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg on potential serum PD biomarkers of safety and efficacy in ambulant boys ages 4 to <7 years with DMD; and
7. To determine if candidate genetic modifiers of DMD (gene polymorphisms associated with disease severity, or response to glucocorticoid treatment) are similarly associated with vamorolone-treated DMD patients subjects (baseline disease severity, or response to vamorolone or prednisone treatment).

**Study design**

This Phase IIb study is a randomized, double-blind, parallel group, placebo and active-controlled study to evaluate the efficacy, safety, PD, and population PK of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg

versus prednisone 0.75 mg/kg/day and placebo over a Treatment Period of 24 weeks, and to evaluate persistence of effect over a Treatment Period of 48 weeks in ambulant boys ages 4 to <7 years with DMD.

The study is comprised of a 5-week Pretreatment Screening Period, a 1-day Pretreatment Baseline Period, a 24-week Treatment Period #1 (Weeks 1-24), a 4-week Transition Period (Weeks 25-28), a 20-week Treatment Period #2 (Weeks 28 + 1 day to 48), and a 4-week Dose-tapering Period (Weeks 49-52).

Subjects will be randomized to one of six treatment groups in a 2:2:1:1:1:1 ratio, where the two prednisone groups in Treatment Period #1 (Groups 3 and 4) will be combined and the two placebo groups in Treatment Period #1 (Groups 5 and 6) will be combined, effectively resulting in a 1:1:1:1 randomization (vamorolone 2.0 mg/kg/day : vamorolone 6.0 mg/kg/day : prednisone 0.75 mg/kg/day : placebo) for Treatment Period #1. See Table 6 in the protocol.

Subjects will be stratified based on age at study entry (<6 vs. * 6 years). During the 4-week Transition Period between Treatment Period #1 and Treatment Period #2, all subjects will continue on the same oral suspension (vamorolone 2.0 mg/kg or 6.0 mg/kg, or matching placebo) they received during Treatment Period #1 and all subjects will have their tablet dose tapered to zero. Thus, subjects randomized to receive vamorolone during Treatment Period #1 (Groups 1 and 2) will continue to receive vamorolone at the same dose, while subjects randomized to receive prednisone will have their dose tapered to zero, and subjects randomized to placebo will continue to receive placebo.

At the end of the Treatment Period #2, subjects will be given the option of enrolling into a long-term extension study or to transition to standard of care treatment for DMD (may include glucocorticoids).

**Intervention**

Each subject will be treated daily for 24 weeks with vamorolone (investigational medicinal product), prednisone (active control) or a placebo in a randomized, double-blind setting see Table 6 in the protocol.

After the first Treatment Period of 24 weeks and a 4-week Transition Period, subjects will continue in Treatment Period #2 in which all subjects will take 2.0 mg/kg of 6.0 mg/kg vamorolone daily.

At the end of the Treatment Period #2, subjects will be given the option of enrolling into a long-term extension study or to transition to standard of care treatment for DMD

**Study burden and risks**

Risks of vamorolone or prednisone: adrenal suppression, elevated liver enzymes

Prednisone Risks: Weight gain, Changes in the facial appearance (puffy face), Slow growth, Increased risk of fractures, Behavioral changes, Increased blood pressure, Upset stomach, Development of eye cataracts or increased eye pressure (glaucoma), Weakened immune system (more likely to catch an infectious disease). There may be changes in the skin such as excessive hair growth, acne, skin thinning and easy bruising.

Risks of Blood Draws: soreness or bruising at the site of the needle insertion.

Risk of Electrocardiography: Rarely, this test may cause irritation to the skin under the electrodes.

Risk of DEXA scan and Spine X-Ray: exposure to a small amount of radiation.

Risks of Muscle Strength, Functional, and Timed Tests: fatigue, muscle soreness,

Risks of ACTH stimulation test: a small bruise which may appear at the place where the needle was inserted, a small risk of developing symptoms of adrenal insufficiency.

## Contacts

**Public**
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**Scientific**
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US

## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Children (2-11 years)

## Inclusion criteria

1. Subject's parent(s) or legal guardian(s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements
2. Subject has a centrally confirmed (by TRiNDS central genetic counselor[s]) diagnosis of DMD as defined as:
* Dystrophin immunofluorescence and/or immunoblot showing complete dystrophin deficiency, and clinical picture consistent with typical DMD, OR
* Identifiable mutation within the DMD gene (deletion/duplication of one or more exons), where reading frame can be predicted as 'out-of-frame', and clinical picture consistent with typical DMD, OR
* Complete dystrophin gene sequencing showing an alteration (point mutation, duplication, other) that is expected to preclude production of the dystrophin protein (i.e. nonsense mutation, deletion/duplication leading to a downstream stop codon), with a clinical picture consistent with typical DMD;
3. Subject is *4 years and <7 years of age at time of enrollment in the study;
4. Subject weighs >13.0 kg and *39.9 kg at the Screening Visit;
5. Subject is able to walk independently without assistive devices;
6. Subject is able to complete the Time to Stand Test (TTSTAND) without assistance in <10 seconds, as assessed at the Screening Visit;
7. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. [Notes: Serum gamma glutamyl transferase (GGT), creatinine, and total bilirubin all must be * upper limit of the normal range at the Screening Visit. An abnormal vitamin D level that is considered clinically significant will not exclude a subject from randomization.];
8. Subject has evidence of chicken pox immunity as determined by:
- Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period, OR
- Documentation, provided at the Screening Visit, that the subject has had 2 doses of varicella vaccine, with or without serologic evidence of immunity; the

second of the 2 immunizations must have been given at least 14 days prior to randomization.
9. Subject is able to swallow tablets, as confirmed by successful test swallowing of placebo tablets during the Screening Period; and
10. Subject and parent(s)/guardian(s) are willing and able to comply with scheduled visits, study drug administration plan, and study procedures.

## Exclusion criteria

1. Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression;
2. Subject has current or history of chronic systemic fungal or viral infections;
3. Subject has had an acute illness within 4 weeks prior to the first dose of study medication;
4. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), mexrenone (mexrenoate potassium) within 4 weeks prior to the first dose of study medication;
5. Subject has a history of primary hyperaldosteronism;
6. Subject has evidence of symptomatic cardiomyopathy [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary];
7. Subject is currently being treated or has received previous treatment with oral glucocorticoids or other immunosuppressive agents [Notes: Past transient use of oral glucocorticoids or other oral immunosuppressive agents for indication other than DMD for no longer than 1 month cumulative, with last use at least 3 months prior to first
dose of study medication, will be considered for eligibility on a case-by case basis, unless discontinued for intolerence. Inhaled and/or topical glucocorticoids prescribed for an indication other than DMD are permitted if last use is at least 4 weeks prior to first dose of study medication or are administered at stable dose beginning at least 4 weeks prior to first dose of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
8. Subject has an allergy or hypersensitivity to the study medication or to any of its constituents;
9. Subject has used idebenone within 4 weeks prior to the first dose of study medication;
10. Subject has severe behavioural or cognitive problems that preclude participation in the study, in the opinion of the Investigator;
11. Subject has previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up will be correctly completed or impair the assessment of study results, in the opinion of the Investigator;
12. Subject is taking (or has taken within 4 weeks prior to the first dose of

study medication) herbal remedies and supplements which can impact muscle strength and function (e.g. Co-enzyme Q10, Creatine, Proglandine etc);
13. Subject is taking (or has taken within 3 months prior to the first dose of study medication) any medication indicated for DMD, including Exondys51 and Translarna;
14. Subject has been administered a live attenuated vaccine within 14 days prior to the first dose of study medication;
15. Subject is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to the first dose of study medication;
16. Subject has a sibling who is currently enrolled in any vamorolone study or Expanded Access Program, or who intends to enroll in any vamorolone study or Expanded Access Program during the subject's participation in the VBP15-004 study; or
17. Subject has previously been enrolled in the study.
Note: Any parameter/test may be repeated at the Investigator's discretion during Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to a transient condition which would prevent the subject from participating, such as an upper respiratory tract infection or injury, or if ineligible due to negative antivaricella IgG antibody test result.

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 09-12-2019 |
| Enrollment: | 10 |

| | |
|---|---|
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Prednisone |
| Generic name: | Corticosteroids |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Vamorolone |
| Generic name: | Vamorolone |

## Ethics review

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|---|---|
| Approved WMO Date: | 25-02-2019 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 10-10-2019 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 21-10-2019 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 31-03-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |

| | |
|---|---|
| | metc-ldd@lumc.nl |
| Approved WMO<br>Date: | 03-06-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |
| Approved WMO<br>Date: | 10-06-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |
| Approved WMO<br>Date: | 27-08-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |
| Approved WMO<br>Date: | 06-10-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |
| Approved WMO<br>Date: | 18-11-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |
| Approved WMO<br>Date: | 31-03-2021 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |

| | |
|---|---|
| | metc-ldd@lumc.nl |
| Approved WMO Date: | 29-07-2021 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |
| Approved WMO Date: | 19-08-2021 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2017-002704-27-NL |
| ClinicalTrials.gov | NCT03439670 |
| CCMO | NL65653.058.19 |

# Study results

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|---|---|
| Date completed: | 22-04-2021 |

Actual enrolment: 7

**Summary results**
Trial is onging in other countries