Vamorolone Phase 2b (VISION-DMD)

A Study to Assess the Efficacy and Safety of Vamorolone in Boys With Duchenne Muscular Dystrophy (DMD)

Hub Summary

This Phase 2b study is designed to evaluate the efficacy, safety pharmacodynamics and pharmacokinetics of vamorolone in comparison to corticosteroids and placebo treatments over a 24 week period. The study will also evaluate the persistence of the effect of vamorolone over a period of 48 weeks.

The study is designed to compare 2 different doses of Vamorolone to a standard dose of corticosteroids (prednisone at 0.75 mg/kg/day) and to a placebo. Across all sites, this trial will be recruiting a total of 120 ambulant DMD patients ages 4 to <7 years.

Study Number: NCT03439670

Description by ReveraGen BioPharma

This Phase IIb study is a randomised, 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.

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.

A total of approximately 120 subjects will be randomized (2:2:1:1:1:1) to treatment.

The prednisone group will be used as an active control comparison for safety and efficacy endpoints as requested by the European Medicines Agency (EMA). The placebo group will be used as comparator for efficacy endpoints (superiority model) as requested by the EMA and Food and Drug Administration (FDA) protocol advisory board.

At the end of the Treatment Period #2, subjects will be given the option of enrolling into a long-term extension study (VBP15-005) or to transition to standard of care treatment for DMD (may include glucocorticoids). Subjects completing VBP15-004 and enrolling directly into VBP15 005 will not need to taper their vamorolone dose prior to enrolment into VBP15 005. All other subjects will begin a 4 week double blind Dose tapering Period during which the dose of study medication will be progressively reduced and discontinued.

Primary Outcome Measures

- Muscular function measured by Time to Stand Test (TTSTAND) (24 weeks)
- Body Size as measured by body mass index (BMI) x-score (24 weeks)

Secondary Outcome Measures

- Safety measure by Treatment emergent adverse events (TRAEs) and serious adverse events (SAEs) by organ system class (SOC).
- Safety measure assessed by sitting blood pressure.
- Safety measure assessed by heart rate.
- Safety measured assessed by respiratory rate.
- Safety measure assessed by body temperature.
- Safety measure assessed by height

Trial Status
Trial complete

UK Locations
London - GOSH, Trial complete/terminated, Alder Hey, Trial complete /terminated, Birmingham, Trial complete/terminated, Glasgow, Trial complete /terminated, Leeds, Trial complete/terminated, Newcastle, Trial complete /terminated

Trial Sponsor
ReveraGen BioPharma

Phase
2b

Length Of Participation
52 weeks

Recruitment Target
120

Ambulatory
Ambulant

Therapeutic Category
Steroid alternative

Age
4 to 7 years

Mutation Specific
Non-mutation specific therapies

Muscle Biopsy
No Muscle Biopsy Required

MRI
No

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- Cushingoid features measured by the presence of buffalo hump obesity, striations, adiposity, hypertension, diabetes, or osteoporosis
- Safety measure assessed by blood laboratory measures.
- Safety measure assessed by urine laboratory measures.
- Cardiac function measured by 12 lead electrocardiogram (ECG)
- Cardiac function measured by 2-D echocardiogram.
- Safety measure based on dual-energy x-ray absorptiometry (DXA) scan.
- Spine Fracture measured by spine X-ray
- Cataracts measured by the presence of partial or complete opacity of the crystalline lens of one or both eyes.
- Glaucoma measured by measured by ocular pressure.
- Safety measured assessed by Synacthen (ACTH) test
- Efficacy measured by Time to Stand Test (TTSTAND)
- Efficacy measured by Time to Climb (TTCLIMB).
- Efficacy as measured by Time to Run/Walk Test (TTRW).
- Efficacy as measured by total distance traveled in meters, in completing the Six-minute Walk Test (6MWT)
- Efficacy as measured by the North Star Ambulatory Assessment (NSAA)
- Efficacy as measured by hand-held myometry (elbow flexors and knee extensors)
- Efficacy as measured by range of motion in the ankles (ROM)
- Safety as measured by serum pharmacodynamic biomarkers by morning cortisol.
- Safety as measured by serum pharmacodynamic biomarkers by levels of fasting glucose.
- Safety as measured by serum pharmacodynamic biomarkers by levels of fasting insulin.
- Safety as measured by serum pharmacodynamic biomarkers by levels of osteocalcin.
- Safety as measured by serum pharmacodynamic biomarkers by levels of CTX1.
- Safety as measured by serum pharmacodynamic biomarkers by levels of P1NP.
- Safety as measured by serum pharmacodynamic biomarkers by levels of differential lymphocyte percentage.
- Extremity Fracture Questionnaire
- Physical examination findings at each of the pretreatment, on treatment, and post treatment assessment time points determined by change from baseline in physical examination findings, with assessment of clinical significance.

Can I take part?

Inclusion Criteria

- ✔ 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
- ✔ Subject has a centrally confirmed (by TRiNDS central genetic counselor[s]) diagnosis of DMD as defined as:

1. Dystrophin immunofluorescence and/or immunoblot showing complete dystrophin deficiency, and clinical picture consistent with typical DMD, OR
2. 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
3. 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;

- ✔ Subject is 4 years and <7 years of age at time of enrollment in the study;
- ✔ Subject weighs >13.0 kg and 39.9 kg at the Screening Visit;
- ✔ Subject can walk independently without assistive devices;
- ✔ Subject can complete the Time to Stand Test (TTSTAND) without assistance in <10 seconds, as assessed at the Screening Visit;
- ✔ 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. [Note: Serum gamma glutamyl transferase (GGT), creatinine, and total bilirubin all must be upper limit of the normal range at the Screening Visit];
- ✔ 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 at the Screening Visit;
- ✔ Subject can swallow tablets, as confirmed by successful test swallowing of placebo tablets during the Screening Period; and
- ✔ Subject and parent(s)/guardian(s) are willing and able to comply with scheduled visits, study drug administration plan, and study procedures.

Exclusion Criteria

- ✖ Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression;
- ✖ Subject has current or history of chronic systemic fungal or viral infections;
- ✖ Subject has had an acute illness within 4 weeks prior to the first dose of study medication;
- ✖ 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;
- ✖ Subject has a history of primary hyperaldosteronism;
- ✖ Subject has evidence of symptomatic cardiomyopathy [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary];
- ✖ Subject is currently being treated or has received previous treatment with oral glucocorticoids or other immunosuppressive agents [Notes: Past transient use of oral or inhaled glucocorticoids or other oral immunosuppressive agents for indication other than DMD for no longer than 3 months cumulative, with last use at least 3 months (or last use at least one month prior for inhaled glucocorticoids) prior to first dose of study medication, will be considered for eligibility on a case-by-case basis. 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 are anticipated to be used at the stable dose regimen for the duration of the study];
- ✖ Subject has an allergy or hypersensitivity to the study medication or to any of its constituents;
- ✖ Subject has used idebenone within 4 weeks prior to the first dose of study medication;
- ✖ Subject has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the Investigator;
- ✖ 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;
- ✖ 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);
- ✖ 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;
- ✖ 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; or
- ✖ Subject has previously been enrolled in the study.

For contact details and to find out more, please refer to dmdhub.org.

Duchenne UK