A Randomized, Double-Blind, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Taldefgrobep Alfa in Ambulatory and Non-Ambulatory Participants with Spinal Muscular Atrophy with Open-Label Extension (RESILIENT)

Published: 28-09-2022
Last updated: 05-10-2024

This study has been transitioned to CTIS with ID 2024-511852-42-00 check the CTIS register for the current data. Primary Objective:To evaluate the efficacy of taldefgrobep alfa in participants who are already taking a stable dose of nusinersen or…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53477

Source
ToetsingOnline

Brief title
RESILIENT

Condition

- Neurological disorders congenital
- Muscle disorders

Synonym

RESILIENT

Research involving
Human

Sponsors and support

Primary sponsor: Biohaven Pharmaceuticals, Inc
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Efficacy, MFM-32, Spinal Muscular Atrophy, Taldefgrobep Alfa

Outcome measures

Primary outcome

Change from baseline in the MFM-32 at Week 48

Secondary outcome

Change from baseline in the RULM at Week 48;

Change from baseline in the RHS at Week 48;

Safety and tolerability assessments including change in lean body mass and bone mineral density on DXA scan from baseline at Week 48 and Tanner staging for puberty monitoring, monitoring of injection acceptability assessments, and frequency of unique subjects with: new or worsening lab abnormalities, treatment related adverse events, serious adverse events, and adverse events leading to discontinuation;

Trough plasma concentrations of taldefgrobep alfa and pharmacokinetic parameters estimated with population PK modeling.

Study description

Background summary

Taldefgrobep alfa is expected to preserve and improve muscle strength primarily by increasing the size of existing muscle fibers.

Data from a first-in-human, combined single and multiple ascending dose (SAD/MAD) study in normal healthy volunteers (NHVs) (CN001-001) indicate that taldefgrobep alfa administered SC at single doses up to 180 mg, and multiple doses up to 180 mg weekly (Q1W) and of 45 mg
every 2 weeks of are generally safe and well tolerated. Pharmacokinetic (PK) data indicate that plasma concentrations of total taldefgrobep alfa (serum free taldefgrobep alfa plus taldefgrobep alfa-myostatin complex) increase in a dose related fashion. Similarly, the extent and duration of
serum free myostatin suppression increases in a dose related fashion. Treatment with 5 weekly doses of 45 mg or more of taldefgrobep alfa was associated with increases in thigh muscle volume and total lean body mass in NHVs.

Data from a Phase 1b/2 (CN001-006 [other study identifier WN40226]), multi-site, randomized, placebo-controlled multiple ascending SC dose study to evaluate the safety, tolerability and PK of taldefgrobep alfa in 43 ambulatory boys (>=5 to <11 years of age) with DMD indicate that repeated dosing up to 35 mg or 50 mg (based on body weight) was generally safe and well tolerated in a 24-week double-blind phase and 48-week open-label phase. There was dose dependent suppression of free serum myostatin from baseline and MRI and DXA data was consistent with a positive beneficial effect on muscle health.

A Phase 2/3 (CN001-016 [other study identifier WN40227]) multi-center, randomized, double-blind, placebo-controlled study was conducted to assess the efficacy, safety and tolerability of two different weekly doses of taldefgrobep alfa SC in ambulatory boys (>=6 to <12 years of age) with DMD taking corticosteroids (n=166). Taldefgrobep alfa was generally safe and well-tolerated. A futility analysis based on the primary endpoint of the change from baseline in the North Star Ambulatory Assessment (NSAA) Total Score at Week 48, showed no notable treatment difference either between the pooled treatment group or by assigned treatment (low or high dose) and placebo in the intent to treat population. Thus, the study was terminated.

Based on the available nonclinical and clinical data, no special precautions for taldefgrobep alfa use are indicated. Data from prior clinical studies suggest that taldefgrobep alfa is generally safe and well tolerated. Potential risks of taldefgrobep alfa are consistent with other biologics and include hypersensitivity reactions and immunogenicity.

Current standard of care includes disease modifying therapies which increase SMN protein production, thus improving survival, decreasing the need for respiratory intervention, and significantly improving motor function. Despite these treatments, a high unmet need for safe and effective treatments in SMA remains, as many participants still experience significant weakness, respiratory limitations and reduced levels of function.

Anti-myostatin agents have been tested in many neuromuscular syndromes and diseases to enhance muscle size and performance. Although many of these studies have failed to show clinically statistical significance, recent non-clinical and clinical data have shown that preventing myostatin signalling can lead to therapeutic potential in addressing muscle and bone deficiencies in SMA participants.

Taldefgrobep alfa is a novel anti-myostatin that acts both by binding mature myostatin dimer and also blocking he signaling of the ActIIRb pathway. The probability of success is also improved with the introduction of SMN therapies as standard of care, thereby enhancing the potential for a clinical benefit.

Study objective

This study has been transitioned to CTIS with ID 2024-511852-42-00 check the CTIS register for the current data.

Primary Objective:
To evaluate the efficacy of taldefgrobep alfa in participants who are already taking a stable dose of nusinersen or risdiplam or have a history of onasemnogene abeparvovec-xioi, compared to placebo, measured by change in the 32 item Motor Function Measure (MFM-32) total score
between Baseline and Week 48.

Secondary Objectives:
To compare the efficacy of taldefgrobep alfa to placebo using the Revised Upper Limb Module (RULM);
To compare the efficacy of taldefgrobep alfa to placebo using the Revised Hammersmith Scale (RHS);
To assess the safety and tolerability of taldefgrobep alfa including change from baseline in lean body mass and bone mineral density on DXA scan at Week 48, Tanner staging for puberty monitoring, new or worsening lab abnormalities, injection acceptability assessment, treatment-related adverse events (AEs), serious AEs, and AEs leading to discontinuation;
To assess pharmacokinetic (PK) parameters of taldefgrobep as estimated with population PK
modeling.

Exploratory Objectives:
To evaluate change in time to run 10 meters as measured by RHS item 19, comparing taldefgrobep alfa and placebo;
To evaluate change in time to rise from floor as measured by RHS item 25, comparing taldefgrobep alfa and placebo;
To evaluate change from Baseline in number of WHO motor development milestones attained;
To evaluate the participant quality of life using the proxy-reported SMAIS-ULM total score comparing taldefgrobep alfa and placebo;

To evaluate the participant quality of life using the self-reported SMAIS-ULM total score comparing taldefgrobep alfa and placebo (for participants age >=12);
To evaluate the caregiver quality of life using the ACEND caregiver-reported total score comparing taldefgrobep alfa and placebo;
To evaluate the change in pulmonary function with % predicted forced vital capacity (ppFVC), maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP);
To evaluate change in lean body mass from baseline on DXA scan, comparing taldefgrobep alfa and placebo;
To assess target engagement and other pharmacodynamic biomarkers;
To assess immunogenicity;
To assess the proportion of participants rated by clinician as improved in the Clinician*s Global Impression of Change (CGI-C) scale comparing taldefgrobep alfa and placebo;
To evaluate relationships between taldefgrobep drug exposure and efficacy and safety
endpoints of interest, as warranted.

Study design

BHV2000-301 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2 arm study designed to assess the efficacy and safety of taldefgrobep alfa in study participants with SMA who are stable on standard of care therapy including risdiplam, nusinersen, or who have a history of treatment with onasemnogene abeparvovec-xioi. Eligible participants will have the opportunity to continue in a 48-week open-label extension (OLE) phase.

Per the protocol, study participants who complete the 48 week Double-blind phase have the option to participate in the 48 week Open Label Extension phase of the study to receive taldefgrobep alfa. A plan to provide taldefgrobep alfa to participants following their completion of the 48 week Open Label Extension is not currently in place, although Biohaven recognizes that this is important. As the study progresses, Biohaven will explore and review potential options and consider an optimal plan for continuation of taldefgrobep alfa to those participants who complete the 48-week Open Label Extension and are determined by the Investigator to be receiving a benefit.

Intervention

A 1-weekly subcutaneous injection of Aldefgrobep Alfa (35 or 50 mg in 0,7 ml, based on subject's weight) or placebo (0,7 ml) for the duration of 48 weeks. Eligible participants will have the opportunity to continue in a 48-week open-label extension (OLE) phase (1-weekly subcutaneous injection of Aldefgrobep Alfa, 35 or 50 mg in 0,7 ml, based on subject's weight).

Study burden and risks

Taldefgrobep alfa is a novel myostatin antagonist that is being developed as a therapeutic to increase muscle mass and strength. The active study drug may help to relieve SMA symptoms.

Burden - Subjects will undergo the following tests/assessments:
(Standard) Physical Examination and physical measurements (height, weight, temperature, blood pressure, heart rate): 6 times (double-blinded phase), 4 times (open-label extension phase);
Venapunction: 6 times (double-blinded phase), 4 times (open-label extension phase);
Subcutaneous injection (IP): 47 times in double-blinded phase and 47 times in open-label extension phase;
DXA scan: 3 times in double-blind phase;
12-lead ECG: 3 times (double-blinded phase), 1 time (open-label extension phase);
Pregnancy test: Monthly home tests (urine) as appropriate and 6 times on site (double-blinded phase) and 4 times during open-label extension phase;
Pubertal status will be assessed (for both male and female participants) according to Tanner staging at Baseline and at least every 12 months until the end of the study participant*s participation in the trial or until the study participant reaches Tanner stage V (whichever comes first). Self-reported Tanner staging or records from pediatric assessments in standard of care settings are acceptable;
Columbia-Suicide Severity Rating Scale (from the age of 6): 6 times (double-blinded phase), 4 times (open-label extension phase);
Efficacy Assessments (MFM-32, RULM, RHS, WHO developmental milestones): 6 times (double-blinded phase), 2 times open-label extension phase;
Efficacy Assessments (SMAIS-ULM, Spirometry, ACEND): 3 times (double-blinded phase), 1 time (open-label extension phase);
CGI-C: 2 times (double-blinded phase), 1 time (open-label extension phase).

Risks/burden related to study treatment:
Prior to the start of this clinical study, a total of 359 participants had received taldefgrobep alfa, including 179 healthy participants and 180 boys with Duchenne Muscular Dystrophy (DMD) and has been generally well tolerated. For additional information, please see the current Investigator Brochure.

The side effects reported in completed studies are listed below by how often they occurred.
Among healthy adult humans who received taldefgrobep alfa administered subcutaneously (SC) at single doses up to 180 mg, and multiple doses up to 180 mg weekly and of 45 mg every 2 weeks, the most common side effects were mild injection site redness and rash. These adverse events did not require stopping of study drug and were not accompanied by systemic signs or symptoms, such as fever or high levels of white blood cells (eosinophilia).

In a clinical trial in boys with DMD 5 to 11 years old on taldefgrobep alfa

doses up to 35 mg or 50 mg (based on body weight) once weekly, the following side effects were seen in those receiving taldefgrobep alfa:

Very common (may affect more than 1 in 10 people, 10%):
• Vomiting (37.2%)
• Swelling of the nose and throat (37.2%)
• Headache (37.2%)
• Upper respiratory tract infection (34.9%)
• Fall (32.6%)
• Fever (30.2%)
• Diarrhea (30.2%)
• Cough (30.2%)
• Injection site bruising (27.9%)
• Injection site inflammation with rash (erythema) (27.9%)
• Injection site redness (27.9%)
• Pain in extremity limb (20.9%)
• Nasal congestion (20.9%)

The most frequently reported side effects thought to be related to study drug treatment were:

Common (may affect up to 1 in 10 people, 10%):
• Injection site rash (7.0%)
• Injection site pain (7.0%)
• Injection site bleeding (4.7%)
• Injection site reaction (4.7%)
• Flushing (4.7%)
• Injection site discomfort (2.3%)
• Injection site itchiness (2.3%)
• Injection site swelling (2.3%)
• Strep throat (2.3%)
• Headache (2.3%)

In a clinical trial in boys with DMD 6-12 years old on taldefgrobep alfa low dose (7.5mg or 15mg) or high dose (35mg or 50mg) based on weight, once weekly, the following side effects were seen (see below):

The most frequently reported side effects thought to be related to study drug treatment were:
Very common (may affect more than 1 in 10 people) by taldefgrobep alfa low and high dose groups:
• Nasopharyngitis (swelling of the nose and throat)
• Injection site erythema (redness)
• Headache
• Fever
• Cough
• Vomiting

• Arthralgia (joint pain)
• Back pain
• Upper respiratory tract infection
• Extremity pain
• Rash
• Upper abdominal pain
• Nausea
• Nosebleeds

Common (may affect up to 1 in 10 people, 10%) by taldefgrobep alfa subdivided into low and high dose groups:
• Back pain (4.4% high dose)
• Upper respiratory tract infection (7.2% low dose)
• Extremity pain (7.2% low dose)
• Rash (7.2% low dose)
• Upper abdominal pain (7.2% low dose)
• Nausea (2.9% low dose)
• Nosebleeds (4.3% low dose)

Studies have shown that there may be a small decrease of immunization effectiveness while taking Taldefgrobep alfa, but this is a small decrease and not expected.

Allergic reaction risks:
There is a small but real risk of allergic reactions that can be life-threatening or fatal.

Risks/burden related to study procedures:
Subcutaneous Injection of Study drug/Placebo - Local pain, bruising, bleeding, blood clot formation, a rash and in rare instances an infection might occur at the site of injection. There is also the possibility of dizziness or fainting while being injected.
Blood Draw - Local pain, bruising, bleeding, blood clot formation, and in rare instances an infection might occur at the site of the needle stick where blood is drawn. There is also the possibility of dizziness or fainting while blood is being drawn.
Electrocardiogram (ECG) - The ECG procedure may cause minimal discomfort during the attachment and removal of the ECG leads to and from the skin (skin irritation from the electrode adhesive or develop contact dermatitis)
DXA Scan - The DXA scan may cause discomfort as the subject will need to be still and may have to hold their breath for a few seconds.
In the DXA exam a small amount of radiation will be used. The amount of radiation (energy) is very small -- less than one tenth the dose of a chest x-ray, and less than a day*s exposure to natural radiation. It is not dangerous if the subject have to have an examination or treatment with radiation for a medical reason.

Benefit and group relatedness:
SMA is an inherited neuromuscular disease characterized by muscle atrophy due to degeneration of lower motor neurons. The primary symptom is severe muscle weakness. Medications recently approved for certain subsets of SMA patients target the Survival Motor Neuron 1 (SMN1) gene
and SMN2 transcript and may help to preserve motor neurons. However, despite the availability of these SOC medications, SMA remains a progressive and debilitating condition. No treatment that specifically targets muscle weakness is currently available. Taldefgrobep alfa is a novel
myostatin antagonist that is being developed as a therapeutic to increase muscle mass and strength. The high unmet need for treatments for SMA, together with the available preclinical and clinical data with taldefgrobep alfa,
provide a compelling and favorable overall benefit-risk assessment for the development of taldefgrobep alfa as a treatment for SMA. The safety monitoring in the planned clinical study will minimize the potential risks to study participants. It is crucial to develop treatment to prevent (further) increase of muscle atrophy as quickly as possible. The study population represents the future target group.

Contacts

Public
Biohaven Pharmaceuticals, Inc

215 Church Street n/a
New Haven CT 06510
US
Scientific
Biohaven Pharmaceuticals, Inc

215 Church Street n/a
New Haven CT 06510
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

* Spinal Muscular Atrophy confirmed by genetic diagnosis of 5qautosomal recessive SMA as well as SMN2 copy number
* Ambulant or non-ambulant
* Treated with an SMA disease-modifying therapy and anticipated to remain on that same treatment regimen and dose throughout the trial, including the following:
i. a stable regimen of nusinersen for 6 months prior to Screening; and/or
ii. a stable regimen of risdiplam, for 6 months prior to Screening; and/or
iii. a single dose of onasemnogene abeparvovec, received at least 2 years prior to Screening.

Exclusion criteria

* Receiving or have received previous administration of anti-myostatin therapies * Weight <15 kg * Respiratory insufficiency, defined by the medical necessity for invasive or non-invasive ventilation for daytime treatment while awake (use overnight or during daytime naps is acceptable) * History of spinal fusion or major surgeries within 6 months prior to screening or planned during the study. Non-surgical adjustments are allowed during the study (such as MAGEC rods). * Presence of an implanted shunt for the drainage of CSF or an implanted central nervous system (CNS) catheter

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-04-2023
Enrollment:	8
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Taldefgrobep Alfa
Generic name:	BHV-2000

Ethics review

Approved WMO Date:	28-09-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-11-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-04-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-03-2024
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2024-511852-42-00
EudraCT	EUCTR2022-000193-25-NL
ClinicalTrials.gov	NCT05337553
CCMO	NL81725.041.22