A Phase 3 Randomized, Double-blind, Placebo-controlled, Multi-center Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys with Duchenne Muscular Dystrophy (DMD)

Published: 21-10-2019
Last updated: 17-01-2025

Primary:• To compare the efficacy of viltolarsen administered intravenously (IV) at weekly doses of 80 mg/kg over a 48-week treatment period vs. placebo controls in ambulant boys ages 4 to

Ethical review	Approved WMO
Status	Completed
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON52888

Source
ToetsingOnline

Brief title
NS Pharma - NS-065/NCNP-01-301 - VIL301

Condition

- Muscle disorders

Synonym
DMD, Duchenne Muscular Dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: NS Pharma, Inc.
Source(s) of monetary or material Support: NS Pharma;Inc.

Intervention

Keyword: Ambulant boys, DMD, Phase 3, Viltolarsen

Outcome measures

Primary outcome

• TTSTAND at 48 weeks of treatment

Secondary outcome

Hierarchical analysis at 48 weeks treatment of the following strength and endurance measures:

• TTRW

• 6MWT

• NSAA

• TTCLIMB

• Quantitative muscle strength measured by hand-held dynamometer (elbow extension, elbow flexion, knee extension and knee flexion on the dominant side only)

• Vital signs (blood pressure, heart rate, respiratory rate, and body temperature [modality for determining temperature should be consistent for each participant at all assessment time points throughout the study])

• Physical examination

• Clinical laboratory tests:

• Hematology and clinical chemistry

• Urinalysis

• Urine cytology

• Exogenous tracer glomerular filtration rate (GFR)

• Antibodies to dystrophin and viltolarsen

• 12-lead electrocardiogram (ECG)

• Clinical signs and symptoms (AEs and SAEs)

• Grading of clinical and clinical laboratory AEs will be according to the

Common Terminology Criteria for Adverse Events (CTCAE), v.4.03

Study description

Background summary

DMD is a disorder of progressive weakness leading to severe disability and ultimately death. Patients with DMD have mutations in dystrophin, a key muscle protein. For making proteins our body uses a template (mRNA). DMD mutations disrupt this template, leading to incorrect or no protein assembly with as result a deficiency of the dystrophin protein. At present, glucocorticoid (GC) medication is the only treatment that has been shown to slow the decline of strength and function in DMD patients, however, this treatment can have significant side effects. New therapies based on specific genetic makeups are in development. Viltolarsen is designed to interact with the template used for making the dystrophin protein and to correct for the errors introduced by these mutations.
The purpose of this study is to investigate how safe and effective the new medicine viltolarsen is for the treatment of DMD. Doctors cannot prescribe viltolarsen yet (outside a study). The efficacy of viltolarsen will be compared to the efficacy of a placebo. A placebo is a medicine without any active ingredient. It is a *fake* medicine.

Study objective

Primary:
• To compare the efficacy of viltolarsen administered intravenously (IV) at weekly doses of 80 mg/kg over a 48-week treatment period vs. placebo controls

in ambulant boys ages 4 to <8 years with DMD using the Time to Stand Test (TTSTAND) as a measure of strength and function.

Secondary:
• To compare the efficacy of viltolarsen administered IV at weekly doses of 80 mg/kg in ambulant boys ages 4 to <8 years with DMD over a 48-week treatment period vs. placebo controls using hierarchical strength and endurance outcomes
• To evaluate the safety and tolerability of viltolarsen administered IV at weekly doses of 80 mg/kg in ambulant boys ages 4 to <8 years with DMD

Exploratory:
• To evaluate health-related quality of life impact of viltolarsen treatment on participant*s DMD.

Study design

This Phase 3 study is a randomized, double-blind, placebo-controlled, multi-center study in ambulant boys ages 4 to <8 years with DMD receiving 80 mg/kg viltolarsen administered IV weekly over a 48-week treatment period. Participants are randomly assigned to either 80 mg/kg/week viltolarsen or placebo in a 1:1 ratio.

Group 1:
• 37 participants
• Viltolarsen 80mg/kg/week

Group 2:
• 37 participants
• Placebo

Intervention

Intravenous administration of the study drug.

Study burden and risks

Burden: 50 visits to the clinic, 1 phone call, renal ultrasounds, performing function and strength tests, collecting blood and urine samples and completing 2 questionnaires, undergoing ECGs and GFR assessment with an exogenous tracer

Risks: side effects related to the study drug and risks associated with other study procedures.

The most common side effects of the study medicine (vitolarsen) are listed below

Diastolic blood pressure increased (5%), Changes in kidney function (43%), Immune/allergic symptoms including rash and joint pain (7%), Impaired ability of the heart to adequately pump blood through the body (7%), Infections (48%). Cancer risk of Viltolarsen is unknown and is currently being investigated in animal experiments. The potential risk in humans, however, cannot be excluded at the present time.

The study medicine may cause also side effects that are unknown.

The procedures and tests performed in this study have several risks which are listed below:

1. Risks of receiving an infusion: A rash or pain at the site of the infusion, infection can also happen at the infusion site including redness, swelling, and fever. Standard of care procedures for infusions will be followed to minimize any risk of infusion specific related side effects.
2. Risks of port placement: The risks of the surgery to have the port placed include bruising, scarring, prolonged bleeding from the operation site and infection. Port placement will require anaesthesia. Additional risks of having a port include clots forming in the port, failure of the port device so that it needs to be removed or replaced, introduction of air between the lungs and the chest wall such that the lungs collapse, and injury to a major blood vessel. As with any surgery, there may be other unexpected risks or complications of this surgery that are uncommon but serious, including death.
3. Risks of port use: The risks include infections, clots forming in the port or in his vein (for example the vein that carries blood to his heart), a change in position of the port so that it no longer works well or failure of the port device so that it needs to be removed or replaced. Infection can become a serious complication that in rare cases can lead to sepsis, shock, and/or death. You and your child will be trained in the proper use and care of a port to reduce these risks and to watch for any problems.
4. Risks of anaesthesia in DMD: As DMD affects the muscles, patients with DMD have an increased risk of breathing distress from anaesthesia. General anaesthesia may have increased risks including heart complications and death from general anaesthesia. The study doctor will provide special instructions to the surgeon performing the port placement, the selection of anaesthesia will be discussed with you, and all steps to reduce risks will be taken.
5. Risks of blood sample collection: Risks associated with drawing blood from his arm include momentary discomfort and/or bruising. Infection, excess bleeding, and/or fainting are also possible, although unlikely. Rarely, a more serious injury, such as bleeding under the skin (hematoma) may develop. To reduce discomfort a local numbing cream may be applied. The side effects that may be associated with the numbing cream include lack of sensation to the area where the cream is applied.
6. Renal Ultrasound Risks: There are no known risks. Discomfort is uncommon, but your child will feel some pressure, and may need to drink extra fluids to have a full bladder. Sometimes, an ultrasound may not be able to obtain the

pictures your study doctor needs, so other imaging tests may have to be obtained.
7. Risk of electrocardiography: This test may cause irritation to the skin where the electrodes are placed.
8. Risk of Exogenous tracer GFR test: For this test it might be necessary to inject a very small amount of radioactive tracer (depending of the procedure at your child*s hospital) in order to measure your child*s GFR. The very small risk from this is outweighed by the information that will be gained by the measurement. It is very unlikely that your child will feel any side-effects after the test, but if you think he has please let your child*s doctor know.
9. Risks of strength and function tests: It is possible that these tests could make your child more tired than after a regular (non-research) doctor*s visit. There is also a small risk of falling, shortness of breath, or muscle soreness.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Participant*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. Participant has a confirmed diagnosis of DMD defined as:
a. Participant is male with clinical signs compatible with DMD; and
b. Participant has a confirmed DMD mutation(s) in the dystrophin gene that is amenable to skipping of exon 53 to restore the dystrophin mRNA reading frame including determination of unambiguously defined exon boundaries (using techniques such as Multiplex Ligation-dependent Probe Amplification [MLPA], comparative genomic hybridization [CGH] array or other techniques with similar capability)
3. Participant is >= 4 years and <8 years of age at time of first infusion in the study
4. Participant is able to walk independently without assistive devices
5. Participant is able to complete the TTSTAND without assistance in <10 seconds, as assessed at the Screening Visit and the Pre-infusion Visit (Note: The TTSTAND performed independently from the NSAA should be used to determine eligibility)
6. Participant and parent(s)/guardian(s) are willing and able to comply with scheduled visits, study drug administration plan, and study procedures
7. Participant must be on a stable dose of glucocorticoid (GC) for at least 3 months prior to first dose of study drug and is expected to remain on the stable dose of GC treatment for the duration of the study

Exclusion criteria

1. Participant has current or history of chronic systemic fungal or viral infections
2. Participant has had an acute illness within 4 weeks prior to the first dose of study drug based on the Principal Investigator*s judgment/discretion
3. Participant has evidence of symptomatic cardiomyopathy (Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary)
4. Participant has an allergy or hypersensitivity to the study drug or to any of its constituents
5. Participant has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the investigator
6. Participant has a previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect participant 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
7. Participant has had surgery within the 3 months prior to the first anticipated administration of study drug or surgery is planned for anytime during the duration of the study
8. Participant has positive test results for hepatitis B antigen, hepatitis C antibody or human immunodeficiency virus (HIV) antibody at screening. (Note: A positive hepatitis C antibody result is acceptable if accompanied by a negative hepatitis C RNA test and normal bilirubin and gamma glutamyl transferase results.)
9. Participant is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to the first dose of study drug or within 5 times the half-life of a medication, whichever is longer
10. Participant was previously enrolled in an interventional study of viltolarsen
11. Participant is currently taking any other exon skipping agent or has taken any other exon skipping agent within 3 months prior to the first dose of study drug
12. Participant has taken any gene therapy
13. Participant is currently taking idebenone, anabolic steroids (e.g., oxandrolone), or products containing resveratrol or adenosine triphosphate, or has taken such within 3 months prior to first dose of study drug. Coenzyme Q10 or creatine are permitted only if the participant is receiving a stable dose for at least 3 months prior to the first dose of study drug and for the duration of the study
14. Note: There is no exclusion criterion #14. This criterion was removed from the protocol with Amendment 4 (version 3.0, dated 08 January 2021); however, the numbering was maintained to avoid documentation errors;
15. Participant has hydronephrosis, hydroureter, renal or urinary tract calculi, or ureteral stenosis by medical history or renal ultrasound.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-09-2020
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Viltolarsen
Generic name:	Viltolarsen

Ethics review

Approved WMO Date:	21-10-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-03-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-05-2020

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	17-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2019-002076-13-NL
CCMO	NL70538.000.19

Study results

Date completed: 19-10-2023

Results posted: 13-11-2024

Actual enrolment: 10

First publication
06-11-2024