A Multicenter, Open-Label Extension Study of WVE-210201 in Patients previously enrolled in WVE-DMDX51-001

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Primary objective:• To evaluate the safety and tolerability of WVE-210201Secondary objectives:• To evaluate the effect of WVE-210201 on dystrophin production• To evaluate the concentration of WVE-210201 in plasma following treatment with WVE-210201...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON48665

Source
ToetsingOnline

Brief title
WVE-DMDX51-002

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
DMD, Duchenne Muscular Dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Wave Life Sciences Ltd.
Source(s) of monetary or material Support: Wave Life Sciences Ltd.

Intervention

Keyword: Duchenne Muscular Dystrophy, Open Label Extension Study, WVE-210201

Outcome measures

Primary outcome

Safety:

To assess the safety and tolerability of WVE-210201, the following will be monitored and collected:

1. Adverse events (AEs)

2. Physical examination findings, including vital signs

3. Safety laboratory tests (hematology, chemistry, coagulation, urinalysis, complement etc.)

4. Electrocardiograms

5. Echocardiograms

WVE-210201 concentration in plasma and urine:

1. Blood samples will be collected for determining plasma concentration of WVE-210201.

2. Urine samples will be collected for determining concentration of WVE-210201

Immunogenicity:

1. Blood samples will be collected for assessing anti-drug and anti-dystrophin antibodies in plasma

Pharmacodynamic Assessments:

1. Dystrophin protein levels and exon skipping will be assessed using muscle

biopsy samples

Measurements of Motor Function

1. Performance of the Upper Limb (PUL, Version 2.0)

2. Respiratory function tests (peak flow rate [PFR], cough peak flow [CPF], and

forced vital capacity [FVC])

3. Upper limb proximal strength assessed by handheld myometer

4. North Star ambulatory assessments

5. Lower limb motor function by timed function tests (including 10-meter

walk/run time, sit to stand from

chair, 4-stair climb time, and time to rise from the floor)

Secondary outcome

-

Study description

Background summary

Duchenne Muscle Dystrophy (DMD) is a disease caused by a mutation in the dystrophin gene. The dystrophin protein is important for protecting the muscles from stress and damage.
In DMD patients, one or more of the exons in the dystrophin gene are missing. As a result, the gene cannot give proper instructions for making dystrophin. Because of this mutation DMD patients are not able to make enough working dystrophin which is needed to help protect their muscles from damage.
WVE-210201 is designed to skip a specific part of the dystrophin gene (the instructions for making dystrophin protein) called exon 51. In people with DMD who are missing certain exons of the dystrophin gene, skipping exon 51 may allow the body to produce a shortened but still working form of the dystrophin

protein. This may result in improved muscle function in people with DMD.

Study objective

Primary objective:
• To evaluate the safety and tolerability of WVE-210201

Secondary objectives:
• To evaluate the effect of WVE-210201 on dystrophin production
• To evaluate the concentration of WVE-210201 in plasma following treatment with WVE-210201
• To evaluate the concentration of WVE-210201 in urine following treatment with WVE-210201

Exploratory Objectives:
• To assess the effect of WVE-210201 on motor function and strength

Study design

This is an open-label extension study (OLE) to evaluate the safety, tolerability, pharmacodynamics, pharmacokinetics and exploratory functional effects of multiple doses of WVE-210201 in male pediatric patients with DMD amenable to exon 51 skipping intervention. Up to 40 male patients, who have successfully completed the WVE-DMDX51-001 study will be enrolled in the open label extension (OLE) study in North America and the European Union (EU).
Both ambulatory and non-ambulatory patients will be enrolled in this study. The study will include a Screening Visit (up to 4 weeks), Treatment Visits for 13 weeks, and Follow-up for 12 weeks.
Written informed consent (and minor assent when applicable) will be obtained from a patient*s parent or legal guardian (and the patient as applicable) prior to participation in this study.
Each patient will receive WVE-210201 once every week for 13 weeks. Patients will be assessed for safety and tolerability, pharmacodynamics, and muscle function and strength. Blood and urine samples will be collected for measuring concentrations of WVE-210201.

Screening Period
The Screening period is intended to allow determination of patient eligibility for the study. It will begin when the study informed consent is signed by the patient and/or parent or legal guardian

(as appropriate). In addition, the
patient may be required to provide assent (as applicable). Patients who have successfully completed the
Phase 1 trial (WVE-DMDX51-001), will be eligible to participate. However, they will need to be re-evaluated for
certain eligibility criteria.The Screening period may last up to 4 weeks (28 days). Patients may start screening for the OLE study after a
minimum of 2 weeks from the last follow-up visit in the Phase 1 study (Day 85). If the Day 85 visit for the Phase
1 trial, WVE-DMDX51-001, was completed within 4 weeks prior to Day 1 of this study, the applicable Phase 1
Day 85 values may be used for the Screening visit values in this study. The required screening evaluations are
outlined in the Schedule of Assessments (Table 2). Screening assessments can occur on multiple days, provided
they are within the Screening period. The Investigator will determine whether patients meet eligibility criteria
and will collect the demographic and medical data permitting full characterization of the patient.

Treatment
In the OLE study, all patients will receive weekly intravenous (IV) doses of WVE-210201 for 13-weeks at one of
the four following dose levels: 1, 2, 5 and 10 mg/kg. Patients receiving 0.5 mg/kg in the Phase 1 study will be
enrolled in the 1 mg/kg cohort of the open label extension (OLE) study. All other dose cohorts will receive
WVE-210201 according to their cohort assignment in Phase 1.
After the first treatment, patients will remain in the clinic for 24 hours postdose for additional safety assessments.
Patients will return to the clinic weekly for WVE-210201 administration through the planned end of treatment
(EOT) period (until Day 92 [±3 days]). On each dosing day, patients will undergo predose and postdose safety
assessments. Additional safety assessments, pharmacodynamic assessments, and muscle strength and functional
assessments will be done throughout the study. Blood and urine samples will be collected for measuring WVE-
210201 concentrations.
The effect of WVE-210201 treatment on dystrophin protein level, dystrophin localization and exon-skipping will
be analyzed using muscle biopsy samples. Blood samples will also be collected for immunogenicity analysis.

Biopsy
Open muscle biopsies will be collected from the deltoid muscle at baseline and at the end of treatment (Day 92).

Needle biopsies will be collected from the tibialis anterior (TA) muscle at baseline and at the end of treatment.
The baseline biopsies must be collected at least 2 weeks prior to Day 1, if the patient is otherwise eligible to
participate in the study.

Follow-up Phase
Assessments of patient safety will be conducted during a 12-week follow up phase in which no treatment with
WVE-210201 will be administered. Visits will occur every 4 weeks during this period (up to Day 176 ±3 days)
after the last dose of WVE-210201.
Early Termination
Early termination assessments will be done according to the study design (Table 2). If the patient terminates
before Day 30, urine and blood samples (planned for Day 30) will also be collected. If a patient terminates prior
to the Day 92 visit (±3 days), all assessments planned for the Day 92 visit including collection of muscle biopsies
will be performed at the early termination (ET) visit. In addition, hematology and clinical chemistry samples
(planned for Day 85) will be collected. If a patient terminates after Day 120, ECHO will not need to be repeated.

Intervention

WVE-210201 will be provided as a solution for dilution for infusion. In this OLE study, all patients will receive
weekly IV doses of WVE-210201 for 13 weeks at one of the following four dose levels: 1, 2, 5 and 10
mg/kg. The route of administration will be IV. The infusion should be administered over approximately a 60
minute period, however at the discretion of the Investigator, and based upon the patient*s cardiopulmonary status,
the infusion time may be extended to a maximum of 3 hours if necessary to avoid volume overload.

Study burden and risks

WVE-210201 is just starting to be studied studied in humans. Therefore there is not much information about the safety of WVE-210201 in humans and the risks are not known. In studies in animals (mice and monkeys) given WVE-210201, it was well tolerated at doses up to those planned for this study.

WVE-210201 is a type of drug called an antisense oligonucleotide. Based on what we know about other similar drugs, there may be a risk of potential damage

to the liver or kidneys, changes in the blood (a decrease in platelets which are involved in clotting and an increase in the time it takes for the blood to clot) and changes in the immune reactions that can cause inflammation. At doses much higher than those that will be used in this study, some mice had damage to their liver after treatment with WVE-210201. These risks will be monitored closely throughout the study and the study treatment will be stopped if the study doctor feels that the subjects' safety may be compromised.

Contacts

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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)
Elderly (65 years and older)

Inclusion criteria

1. Patient and/or parent or legal guardian must have the ability and be willing to provide written informed consent/minor assent prior to any study-related procedures.
2. Patient successfully completed the Phase 1 study with WVE-210201, WVE-DMDX51-001.
3. Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, study restrictions, and all study procedures.
4. Stable pulmonary and cardiac function, as measured by:
a. Reproducible percent predicted forced vital capacity (FVC) >=50%
b. Left ventricular ejection fraction (LVEF) >55% in patients <10 years of age and >45% in patients >=10 years of age, as measured (and documented) by echocardiogram.
5. Sexually mature males must be willing to use contraception for the duration of the study, if the patient is sexually active.
6. Patient and caregivers must agree not to post any study-related information on social media

Exclusion criteria

1. Clinically significant medical finding on the physical examination other than DMD that, in the judgment of the Investigator will make the patient unsuitable for participation in, and/or unable to complete the study procedures.
2. Other prior or ongoing medical conditions including:
a. Acute illness within Screening period;
b. Abnormal physical findings, other than those associated with musculoskeletal findings attributable to DMD.
3. Laboratory abnormality, that, in the Investigator's opinion, could adversely affect the safety of the patient, make it unlikely that the course of treatment or follow up would be completed, or impair the assessment of study results. These include, but are not limited to:
a. Renal insufficiency;
b. Impaired hepatic function as measured by glutamate dehydrogenase (GLDH) >= 2.5x upper limit of normal (ULN) and Bilirubin >= 2x ULN (or INR >= 1.5x ULN;
c. Activated partial thromboplastin time [aPTT] values above the ULN;
d. Platelet count less than lower limit of normal (LLN).
e. Any evidence of clinically significant structural or functional heart abnormality would prohibit participation in this study.
f. Troponin I value above 2x ULN
4. Parent or legal guardian is directly or indirectly involved in the conduct and administration of this study as an Investigator, subinvestigator,

study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	1
Type:	Anticipated

Ethics review

Approved WMO Date:	07-08-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	06-02-2019
Application type:	First submission
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	EUCTR2018-000975-34-NL
CCMO	NL66674.000.18