A Phase 1/2 trial on the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of DYN101 in patients >= 16 years of age with centronuclear myopathies caused by mutations in DNM2 or MTM1

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Primary Objective• To assess the safety and tolerability of 3 single ascending dose (SAD) levels and 3 MAD levels of DYN101.Secondary Objectives• To assess the PK of SAD and MAD of DYN101.• To explore target engagement in muscle of DYN101....

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

Summary

ID

NL-OMON52921

Source
ToetsingOnline

Brief title
Research using an Interventional Treatment for CNM (Unite-CNM)

Condition

- Muscle disorders

Synonym
Muscle illness; Centronuclear myopathies

Research involving
Human

Sponsors and support

Primary sponsor: Dynacure
Source(s) of monetary or material Support: Dynacure

Intervention

Keyword: centronuclear myopathies, DYN101

Outcome measures

Primary outcome

To determine safety and tolerability of SAD and MAD of DYN101, assessed by the number and severity of AEs and SAEs reported from signing of the main ICF onwards until the last trial visit.

Secondary outcome

• To determine PK parameters of DYN101 in plasma following SAD and MAD of DYN101.

• To assess effects of DYN101 (including DNM2 mRNA levels and DYN101 concentration) in muscle biopsies.

Study description

Background summary

In this research study, an investigational drug named DYN101 is being tested for the treatment of centronuclear myopathies (CNMs). DYN101 is an investigational drug as its safety and effectiveness in treating CNMs is still being considered in research studies.

Study objective

Primary Objective
• To assess the safety and tolerability of 3 single ascending dose (SAD) levels and 3 MAD levels of DYN101.

Secondary Objectives
• To assess the PK of SAD and MAD of DYN101.
• To explore target engagement in muscle of DYN101.

Exploratory Objectives
• To investigate the effect of DYN101 treatment on the clinical assessments in various affected domains (respiratory, muscle strength and function, dysphagia).
• To explore the impact of CNM and its treatment on symptoms, functioning, and health-related QoL.
• To assess the presence of anti-drug antibodies (ADA) against DYN101 by collecting blood samples.
• To assess the metabolic profile of DYN101 by collecting blood and urine samples.
• To contribute to the global understanding of CNM and its treatment by collecting blood and muscle samples for further exploratory biomarker/genetic research.

Study design

This is a first-in-human, Phase 1/2, open-label, multi-center trial to evaluate safety, tolerability, PK, PD and preliminary efficacy of DYN101 after SAD and MAD in subjects >= 16 years of age with CNMs caused by mutations in DNM2 or MTM1. Approximately 18 subjects will be selected according to the in- and exclusion criteria. Subjects can be recruited from an ongoing natural history study (NHS), in order to establish solid baseline data, with a minimal requirement of 3 data time points from the NHS.
The trial will consist of a pre-screening consent, a screening period, a run-in period (if applicable), a SAD part with 4 weeks of follow-up after IMP administration and a washout period of at least 12 weeks (followed by follow-up phone calls until the MAD part starts), a MAD part of 12 weeks, and a MAD extension part of 12 weeks. All subjects will participate in the SAD, MAD, and MAD extension parts, unless they withdraw. End-of-treatment assessments will be performed after 24 weeks of MAD treatment have been completed, i.e. at the Week 25 visit. Subjects will be contacted by phone by qualified site personnel 3 months after the last IMP administration, to follow-up on adverse events (AEs) and concomitant medications.

Intervention

Name of Investigational Medicinal Product: DYN101

Study burden and risks

All drugs can cause side effects in some people. You should consider this before you decide to be in the study. To date, there have been no medical research studies using DYN101 in humans.
Although DYN101 is being tested specifically for CNMs, other marketed drugs contain a similar active ingredient. Therefore, the possible side effects you may experience when having treatment with DYN101 may include:
• Temporary increase in liver enzymes (molecules that speed up chemical reactions in the body). This could indicate an inflamed or damaged liver.
• Decreased kidney function. The break down products of DYN101 are excreted by the kidneys.
• Thrombocytopenia - this is a condition caused by a severe decrease in platelet count, which can affect blood clotting and result in bleeding. The symptoms of thrombocytopenia include:
o Nosebleeds, bleeding from gums (either spontaneously or when brushing teeth), dark or bloody stools or blood in urine, vomiting blood, unusually heavy menstrual bleeding (period), or other unusual bleeding (eg, prolonged bleeding after a cut.
o More frequent or easy bruising, or bruising without having had an injury.
o Pinpoint-sized red or purple spots on the skin, in the lining of the mouth, or the whites of the eyes.
o Neck stiffness, unusual drowsiness, severe headaches, or blurred or double vision.
o Severe abdominal pain.

Insertion of Intravenous Catheter
An intravenous catheter will be inserted directly into your vein for administration of DYN101. Local pain, inflammation, bruising, bleeding, blood clot formation, and, in rare cases, an infection might occur in the area where the intravenous catheter is inserted into your vein.

Allergic Reactions
As with taking any drug, there is a risk of developing an allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions include an itchy rash (hives), swelling, shortness of breath, flushing (feeling warm), and a slow heart rate.
Please seek treatment immediately and tell the study doctor and study team if you have any of these symptoms, or any other side effects, during the study.

Blood Sampling
The risks of giving blood include fainting and pain, bruising, swelling, or rarely, infection where the needle was inserted. These discomforts are brief and transient.
The total volume to be collected during your participation in this research study will be no more than 540.5 mL (approximately 36.5 tablespoons) for

mandatory blood samples and an additional 56.5 mL (approximately 4 tablespoons) for optional blood samples; however additional samples may be required depending on the study doctor*s judgement.

Electrocardiogram
The sticky pads placed on your skin for the ECG may sometimes cause some skin irritation, such as redness or itching.

Muscle Biopsy
A small sample of muscle tissue will be surgically removed for testing. Either a needle or an open biopsy will be performed depending on the study doctor*s judgement. If a needle biopsy is conducted, a wide needle will be used to collect a muscle tissue sample. If an open biopsy is conducted, a small cut will be made through the skin to expose and collect a muscle tissue sample. For either procedure you will likely receive a local anaesthetic to numb the area, which may initially sting. At some sites this procedure may be performed in an operating theatre and you may receive a general anaesthetic (in this case, there will be 1 day between the muscle biopsy and administration of DYN101). The limb (arm or thigh) where the biopsy is taken from may take a few days to recover. As this is an invasive procedure, there is a small risk of infection and prolonged bleeding. Bruising is also possible. In addition, as you will be receiving anaesthesia you may experience some initial drowsiness, confusion, dizziness, or nausea. Please inform the study doctor if you have a known allergy to an anasethetic.

Risks to an Unborn Child

Each study visit will include some or all of the following tests/procedures:
• Qualifying Questions
• Demographic Questions
• Medical History Review
• Medication and Treatment Review
• Study Drug Administration
• Physical Examination
• Electrocardiogram (ECG
• Vital Signs
• Liver Ultrasound
• Blood and urine sampling for safety testing
o Blood sampling for platelet count
• Urine Pregnancy Test
• Blood sampling for pharmacokinetic testing
• Blood sampling for antibody testing
• Blood and urine sampling for metabolic profiling
• Side Effect and Adverse Event Review
• Questionnaires
• Respiratory Function Tests
• Muscle Strength and Function Tests

• Eating Assessment Tool
• Muscle Biopsy
• DNA, biomarker, and muscle sampling for exploratory research (optional)

Contacts

Public
Dynacure

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female aged >= 16 years of age* on the date of signing the main ICF. The first subject (i.e. the sentinel subject) in each cohort must be >= 18 years of age.
*for Germany, the subject must be >= 18 years of age in accordance with local and national regulations.
2. Have a documented mutation in DNM2 or MTM1.

3. Platelet count > 150,000/µL,
4. Have a symptomatic CNM in the opinion of the investigator, at least mild to moderately affected, i.e. showing clinical symptoms in at least 2 of the 4 relevant domains that will be investigated in this trial (respiratory function, muscle strength, muscle function, dysphagia), and be ambulatory, i.e. being able to walk 10 steps, if needed with support/assisted. If a subject is non-ambulatory but highly functioning in the view of the investigator, he/she may be included following discussion with the sponsor.
5. Have an understanding, ability and willingness to fully comply with visit frequency, trial procedures and restrictions, including contraceptive requirements.
6. Able to provide written, signed and dated informed consent/assent to participate in the trial. Parental consent (one or both parents) and an assent for subjects < 18 years may be required per local legislation.

Exclusion criteria

1. Clinically significant liver disease.
2. Clinically significant renal disease
3. Presence of significant co-morbidities or conditions other than CNM or clinically significant findings during screening of medical history, physical examination, laboratory testing, vital signs or ECG recording for which, in the opinion of the investigator and the medical monitor, participation would not be in the best interest of the subject (e.g. compromise the safety or well-being) or that could prevent, limit, or confound the protocol-specified assessments (e.g. taking a muscle biopsy).
4. For female subjects of child-bearing potential: pregnant or breastfeeding, or planning to become pregnant during the trial.
5. Current or past abuse of alcohol or recreational/narcotic drugs (with the exception of caffeine and nicotine), which in the investigator*s opinion would compromise the subject*s safety and/or compliance with the trial procedures.
6. Currently enrolled in any interventional trial or scheduled to participate in another trial whilst participating in this trial. Subjects are allowed to participate in registry studies.
7. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the trial, or any condition that presents undue risk from the IMP or procedures.
8. Intake of any disallowed therapies as noted in the protocol within 12 weeks before the planned first IMP administration.
9. Known or suspected intolerance or hypersensitivity to IMP ingredients or closely-related compounds, or history of a significant allergic reaction to IMP ingredients as determined by the investigator, such as anaphylaxis requiring hospitalization.
10. Legally incapacitated or have limited legal capacity. Lack of mental

capacity to fully understand the protocol requirements and complete all study required procedures.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-02-2020
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO Date:	21-06-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-11-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	10-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-10-2021
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-04-2022
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	EUCTR2018-004089-33-NL
CCMO	NL69819.000.19

Study results

Date completed: 22-06-2022

Results posted: 22-12-2022

First publication
15-12-2022