A Phase 2, randomised, double-blind, placebo-controlled, 2-way crossover study to evaluate the efficacy, safety, and tolerability of NMD670 in ambulatory adults with Type 3 spinal muscular atrophy

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This study has been transitioned to CTIS with ID 2024-516321-31-00 check the CTIS register for the current data. The purpose of this study is to measure clinical efficacy on muscle strength and function, safety, and tolerability of NMD670 compared...

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

Summary

ID

NL-OMON56350

Source
ToetsingOnline

Brief title
NMD670/placebo in ambulatory adults with SMA.

Condition

- Neuromuscular disorders

Synonym
5q spinal muscular atrophy, Autosomal recessive proximal spinal muscular atrophy

Research involving

Human

Sponsors and support

Primary sponsor: NMD Pharma
Source(s) of monetary or material Support: Biomedische/farmaceutische industrie: NMD Pharma

Intervention

Keyword: NMD670, Phase 2, Placebo-controlled crossover, Spinal muscular atrophy

Outcome measures

Primary outcome

Primary Objective: To assess changes in muscle strength and function after

NMD670 400 mg bid for 21 days, compared with placebo, in participants with SMA.

Primary Endpoint Change from baseline in 6MWT (total distance, without walking

aids) after 21-day dosing

Secondary outcome

Secondary Objective: To assess changes in muscle strength after NMD670 400 mg

bid for 21 days, compared with placebo, in participants with SMA.

Secondary Endpoint: Change from baseline in individual muscle groups maximum

strength (measured with a dynamometer) after 21-day dosing.

Secondary Objective: To further assess changes in muscle strength and function

after NMD670 400 mg bid for 21 days, compared with placebo, in participants

with SMA

Secondary Endpoint: Change from baseline after 21-day dosing in:

• 6MWT (fatigue index)

• revised Hammersmith scale score

Secondary Objective: To assess changes in neuromuscular junction transmission after NDM670 400 mg bid for 21 days, compared with placebo, in participants with SMA

Secondary Endpoint: Change from baseline in jitter and blocking measured via sfEMG after 21-day dosing

Secondary Objective: To assess the safety and tolerability of NMD670, compared with placebo, over 21-day dosing, in participants with SMA

Secondary Endpoint: AEs, physical examinations, ophthalmological examinations, clinical laboratory parameters, vital signs, ECG, C-SSRS

Study description

Background summary

NMD670 is an inhibitor of skeletal muscle-specific chloride channel protein 1 (ClC-1) that enhances neuromuscular transmission and is being developed by NMD Pharma for the treatment of neuromuscular diseases with neuromuscular junction impairments. Spinal muscular atrophy (SMA) is a genetic disease characterised by loss of motor neurons and impaired motor function and disability because of progressive muscle wasting, in which the neuromuscular junctions are defective in a significant proportion of patients (Arnold et al 2021, Stam et al 2018a). Enhancing the neuromuscular junction function in patients with SMA may improve performance and reduce physical fatigue. This proof-of-concept study aims to evaluate the clinical efficacy on muscle strength and function, safety, and tolerability of NMD670 administered daily for 3 weeks in ambulatory adults with Type 3 SMA.

Study objective

This study has been transitioned to CTIS with ID 2024-516321-31-00 check the CTIS register for the current data.

The purpose of this study is to measure clinical efficacy on muscle strength and function, safety, and tolerability of NMD670 compared with placebo in

ambulatory participants with Type 3 SMA

Study design

• This is a Phase 2, multicentre, randomised, double-blind, placebo-controlled, 2-way crossover study.
• The study will enrol 18 to 75-year-old male and female ambulatory participants diagnosed with Type 3 SMA with neuromuscular junction (NMJ) deficits.
• After screening, eligible participants will be randomised to either receive NMD670 (treatment period 1) followed by placebo (treatment period 2) or receive placebo (treatment period 1) followed by NMD670 (treatment period 2). Both the participant and Investigator will be blinded to treatment sequence assignment and will not know which treatment is given during each treatment period.
• During the study, participants will continue receiving their usual SMA treatment per standard
of care. Participants who receive SMA treatment that is not allowed during the study will not
be eligible to participate in the study.

Intervention

After a screening period of up to 4 weeks, each treatment period in the 2-way crossover design will last 21 days (preceded 1 day before dosing by a baseline visit), separated by a 7-day inter-treatment period and followed by a 7-day follow-up period after the last dose of study
treatment.

The study duration will be approximately 8 to 13 weeks for each participant. The treatment duration will be 3 weeks in each of the 2 treatment periods, separated by a 1-week inter-treatment period.

Participants will be randomised in a 1:1 ratio to receive one of the following treatment
sequences:
• NMD670 (Treatment Period 1) then placebo (Treatment Period 2)
• Placebo (Treatment Period 1) then NMD670 (Treatment Period 2)

NMD670 treatment will consist of oral doses of 400 mg (one 300-mg tablet plus one 100-mg tablet) twice daily (bid) for 21 days. Placebo treatment will follow the same dosing regimen with matching tablets containing placebo.

Study burden and risks

As of November 2022, no serious or severe side effects were reported among 57 healthy subjects and 12 Myasthenia Gravis subjects who received NMD670 in a

clinical study.
The following adverse effects (related or unrelated to the study therapy) were reported in the study. All of them were mild in severity except the events of myotonia (delayed muscle relaxation), gastroenteritis and tooth extraction (all single occurrences) which were moderate in severity at a dose higher than used in the present study:
• Muscular and skeletal symptoms such as flank pain, muscle cramps, muscle and/or bone stiffness, muscle pain, and slowed or impaired relaxation of the muscles
• Gastroenterology symptoms such as abdominal pain, abdominal distension, upper abdominal pain, constipation, diarrhea, indigestion, frequent bowel movement, nausea, and bleeding from the anus
• Nervous system symptoms such as dizziness, headache, partial or total loss of sensation in a part of your body, sensory disturbance, and sleepiness
• General disorders such as fatigue and feeling abnormal
• Skin symptoms such as macular rash
• Events linked to investigations such as alkaline phosphatase increase, creatinine increase, hepatic enzyme increase, and blood pressure decrease or increase.

In addition, a dose related decrease in uric acid levels in blood has been reported in previous studies with NMD670 but this was not considered clinically relevant and not reported as an AE.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

1. Participant must be 18 to 75 years of age inclusive, at the time of signing the informed
consent.
2. Participants who are with a clinical diagnosis of Type 3 SMA.
3. Participants who are ambulatory, defined as being able to walk at least 50 metres without
walking aids.
4. Participant with genetic confirmation of diagnosis (i.e., homozygous deletion of survival of
motor neuron 1 gene [SMN1]).
5. Participant with 3 to 5 copies of survival of motor neuron 2 gene [SMN2].
6. Participants with a MFM-32 dimension 1 score <80% at screening.
7. Participants with >=7% CMAP amplitude decrement at screening (recorded from the trapezius
muscle during repeated nerve stimulation [RNS]).

Exclusion criteria

1. Participants with prior surgery or fixed deformity (scoliosis, contractures) which would
restrict ability to perform study-related tasks.
2. Participants with other significant disease that may interfere with the interpretation of study
data (e.g., other neuromuscular or muscular diseases).
3. Participant with a clinical diagnosis of gout, or with serum uric acid >6.5 mg/dL at screening.
4. Participant with clinically significant ECG abnormalities at screening including PR interval
>=220 msec, irregular rhythms (other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats) in the judgement of the Investigator, or
T-wave configurations are not of sufficient quality for assessing QT interval duration.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-09-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NMD670
Generic name:	NMD670

Ethics review

Approved WMO Date:	09-02-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-06-2023

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-11-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-12-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-02-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-05-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	CTIS2024-516321-31-00
EudraCT	EUCTR2022-002301-24-NL
CCMO	NL82920.058.23