A Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Disease Resulting from Pathogenic Nuclear DNA Mutations (nPMD)

Published: 01-03-2022
Last updated: 30-11-2024

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Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51595

Source
ToetsingOnline

Brief title
SPIMD-301

Condition

- Other condition
- Musculoskeletal and connective tissue disorders congenital

Synonym
energy metabolism disease, nuclear Primary Mitochondrial Disease (nPMD)

Health condition

Primary mitochondrial disease resulting from pathogenic nuclear DNA mutations. Congenital, familial and genetic disorders. Cytoplasmic disorders congenital. Genetic mitochondrial abnormalities NEC.

Research involving
Human

Sponsors and support

Primary sponsor: Stealth BioTherapeutics Inc.
Source(s) of monetary or material Support: Stealth BioTherapeutics Inc.

Intervention

Keyword: Double Blind, Elamipretide/MTP-131, Phase III, Primary Mitochondrial Disease

Outcome measures

Primary outcome

To evaluate the effect of single daily SC administration of elamipretide for 48

weeks on the:

- Distance walked (in meters) on the 6-Minute Walk Test (6MWT)

Secondary outcome

Secondary endpoints:

To evaluate the effect of single daily SC administration of elamipretide for 48

weeks on the:

- Total time (in seconds) the Five-Times Sit-to-Stand Test (5XSST)

- Total time (in seconds) the Triple Timed Up-and-Go Test (3TUG)

- Patient Global Impression of Severity (PGI-S) Scale

Study description

Background summary

All Primary Mitochondrial Diseases (PMDs) share a central pathophysiology of dysfunctional oxidative phosphorylation, with associated impaired bioenergetics and increased oxidative stress. PMDs most commonly affect the body tissues which require the most energy, including the brain, muscle, heart, retina, and cochlea, but can have an extremely variable clinical presentation.

Mitochondria are a dynamic, cellular network of organelles that are centrally involved in cellular metabolism. Mitochondria contain among others an outer membrane that is relatively permeable to small solutes and a tightly regulated inner membrane (IMM) where energy production occurs.
Mitochondria are highly dynamic and adaptive organelles with multiple stress-response mechanisms that enable adaptation to variable bioenergetic demands and dysfunction associated with inherited or acquired genetic mutations, disease, and aging. In nPMD, pathogenic nDNA mutations cause ETC dysfunction and associated oxidative stress which damages cardiolipin, the signature phospholipid of the inner mitochondrial membrane (IMM) essential for mitochondrial and ETC structure, function, and stress-response.

There are currently no approved treatments for nPMD. This has resulted in varied use of different dietary supplements depending on the physician and patient preferences. The need for approved safe and effective treatment options for patients with nPMD remains a serious unmet medical need.

Elamipretide (MTP 131, SS-31) is a first-in-class mitochondrial protective agent that has been shown to improve cell viability and organ function across a spectrum of diseases including skeletal muscle, cardiovascular, renal, metabolic, neurodegenerative, and genetic mitochondrial disease
MTP-131 targets the inner membrane of the parts of cells that produce energy (mitochondria) and stabilizes its structure and function. It is expected that this will result in overall improvement in the function of the cell and organ.

Study objective

The primary objective of this study is to evaluate the effect of single daily SC administration of elamipretide for 48 weeks on the distance walked (in meters) on the 6-minute walk test.

The secondary objectives of this study are:
- To evaluate the effect of single daily SC administration of elamipretide for 48 weeks as measured by changes in the: 1. total time (in sec) the five-times sit-to-stand test; 2. total time (in sec) the triple timed up-and-go

test; and 3. Patiënt Global Impression of Severity (PGI-S) scale
- To evaluate the safety and tolerability of single daily SC doses of elamipretide administered for 48 weeks.

Study design

This randomized, double-blind, parallel-group, placebo-controlled trial will enroll approximately 130 subjects, consisting of 90 subjects who have nPMD associated with pathogenic mutations of the mitochondrial replisome ("replisome-related mutations") for primary analysis and an additional subset of up to 40 subjects who have nPMD associated with other non-replisome-related mutations. In this 48-week, randomized, double-blind, parallel-group, placebo-controlled assessment of the efficacy and safety of single daily SC doses of elamipretide administered as a treatment for subjects who have nPMD, subjects will be randomized (in a ratio of 1:1) to one of two groups:
- 48 weeks of single daily SC doses of 60 mg elamipretide or
- 48 weeks of single daily SC doses of placebo.
Following informed consent, subjects will undergo: a screening period (up to a maximum of 28 days), a treatment period (48 weeks) and a follow-up period (4 weeks).

Intervention

Subjects will be randomized (in a ratio of 1:1) to one of two groups:
- 48 weeks of single daily SC doses of 60 mg elamipretide (MTP-131) or
- 48 weeks of single daily SC doses of placebo.

Subjects randomized to the active arm will receive single daily SC doses of 60 mg MTP-131
Subjects randomized to the placebo arm will receive single daily SC doses of placebo which is composed of sodium chloride, phosphate buffer, and benzyl alcohol similar to excipients used to manufacture the investigational drug but without the active drug substance.

Study burden and risks

The subjects participation in this study will last 56 weeks (13 months). In total the subject will visit the hospital approximately 7 times. Each visit will take between 1 and 3 hours to complete except for the visit in week 12 (4h) and week 24 (8-9h).

Following informed consent, subjects will undergo: a screening period (up to a maximum of 28 days), a treatment period (48 weeks) and a follow-up period (4 weeks).

The following tests and procedures will take place during the hospital visits:

- Physical exam (including body weight and height), vital signs, demographic and medical
- Blood and urine samples are taken. Blood is tested for hepatitis B, C and HIV.
- Pregnancy test for woman of childbearing potential
- ECG
- Questionnaires about how they experience the treatment and their symptoms.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:
1. Willing and able to provide a signed and dated informed consent form (ICF) prior to participation in any trial-related procedures.

2. Agrees, and is able, to adhere to the trial requirements for the length of the trial, including administration of assigned treatment.

3. Is between 18 and 70 years of age at the time of screening.

4. Diagnosed with nPMD with a predominant clinical manifestation of myopathy, which must include progressive external ophthalmoplegia (PEO) and exercise intolerance and/or skeletal muscle weakness, with genetic confirmation of either:
a. Nuclear DNA mutation of the mitochondrial replisome (replisome-related mutation), which include the following genes: POLG 1/2; TWINKLE (C10ORF2); TYMP; DGUOK; TK2; RRM2B; RNASEH1; SSBP; MGME1; DNA2; ANT1 (SLC25A4); SUCLG1; SUCLA2; MPV17
or
b. other pathogenic mutations specific to nuclear DNA.

5. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until 28 days after the last dose of IMP:
a. abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use a highly effective method of contraception should they become sexually active.
b. Relationships with male partners who have been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit).
c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

Note: Non-childbearing potential is defined as surgical sterilization (e.g., bilateral
oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent
cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).

6. Male subjects with female partners of childbearing potential must be willing to use a highly
effective method of contraception from the date they sign the ICF until 28 days after the last
dose of IMP.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. Is unable to perform the 6MWT, 3TUG, or 5XSST functional tests. The use of a gait assist device is allowed; however, use should remain consistent for the entire duration of the trial.

2. Female subjects who are pregnant, planning to become pregnant, or breastfeeding/lactating.

3. Walks < 150 meters or >450 meters during the 6MWT (screening visit only).

4. The estimated glomerulal filtration rate (eGFR) is <30 ml/min/1.73 m2, using the Modification of Diet in Renal Disease (MDRD) study equation (screening visit only).

5. Has undergone an in-patient hospitalization within 30 days prior to screening or has a planned hospitalization or a surgical procedure during the trial, unless in the opinion of the investigator it is concluded that it will not impact the outcome measurements of the trial.

6. Has clinically significant respiratory disease and/or cardiac disease that would
interfere with trial assessments, in the opinion of the Investigator.

7. Has had any prior interventional cardiac procedure (e.g., cardiac catheterization,
angioplasty/percutaneous coronary intervention, balloon valvuloplasty, etc.) within 3 months
prior to screening.

8. Has history of, or current severe neurologic impairment, severe epilepsy, severe
ataxia, or severe neuropathy that may interfere with their ability to complete all trial
requirements, in the opinion of the Investigator.

9. Active malignancy or any other cancer from which the subject has been disease-free for < 2
years. Localized squamous or non-invasive basal cell skin carcinomas are allowed, if
appropriately treated prior to screening.

10. Has had a solid organ transplant.

11. Has been previously diagnosed with human immunodeficiency virus (HIV), hepatitis
B, or hepatitis C infection.

12. Has a history of a systemic eosinophilic illness and/or an eosinophil count

>1,000
cells x106/L at the Screening Visit.

13. Is currently participating or has participated in an interventional clinical trial (i.e.,
investigational product or device, stem cell therapy, gene therapy) within 30 days prior to
current trial; or is currently enrolled in a non-interventional clinical trial that, in the opinion of
the Investigator, may be potentially confounding to the results of the current trial (e.g.,
exercise therapy trial).

14. Has received elamipretide (MTP-131) within the past one year of the Screening Visit.

15. Has a history of active substance abuse during the year prior, in the opinion of the
Investigator.

16. Has any prior or current medical condition that, in the judgment of the Investigator,
would prevent the subject from safely participating in and/or completing all trial assessments
and requirements to the best of their ability.

17. Has a history of allergic reaction to the investigational drug or any of its components.

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):	09-01-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Elamipretide
Generic name:	Elamipretide

Ethics review

Approved WMO Date:	01-03-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-07-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2021-003907-16-NL
CCMO	NL79768.091.22
Other	NTC05162768