A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Assess the Efficacy, Safety, and Tolerability of PXT3003 in Charcot-Marie-Tooth type 1A (CMT1A)

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Primary:To evaluate the efficacy of treatment with PXT3003 (a fixed-dose combination of (RS)-baclofen, naltrexone hydrochloride, and D-sorbitol) compared to placebo in subjects with CMT1A.Secondary: To evaluate the safety and tolerability of PXT3003...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Demyelinating disorders
Study type	Interventional

Summary

ID

NL-OMON52246

Source
ToetsingOnline

Brief title
CLN-PXT3003-06

Condition

- Demyelinating disorders

Synonym
Charcot-Marie-Tooth disease ; Hereditary neuropathy

Research involving
Human

Sponsors and support

Primary sponsor: Pharnext SA
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Charcot-Marie-Tooth, CMT1A, PXT3003

Outcome measures

Primary outcome

The change in the modified Overall Neuropathy Limitation Scale (ONLS) between baseline and the Month 15 visit.

Secondary outcome

The change from baseline to month 15 in the following outcome measures in hierarchical order:

1) 10-Meter Walk Test (10mWT)

2) Quantified Muscular Testing (bilateral foot dorsiflexion dynamometry)

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

4) Patient Global Impression of Change (PGI-C)*

5) Charcot-Marie-Tooth Neuropathy Score, version 2 (CMTNS-v2)

6) Quantified Muscular Testing (hand grip)

* Because the PGI-C is already a change assessment, the change from Baseline is not needed for this endpoint.

Study description

Background summary

Charcot-Marie-Tooth disease type 1A (CMT1A) is a type of inherited neurological

disorder that affects the nerves. CMT1A is caused by having an extra copy of the PMP22 gene. This causes the shell of the nerves to breakdown.
People with this disease experience weakness and wasting (atrophy) of the muscles of the lower legs beginning in teenage years; later they can also have hand weakness and sensory loss. Treatment for this disease may include physical therapy; occupational therapy; braces and other orthopedic devices; orthopedic surgery; and pain medications. These treatments are not sufficient to limit impairment of motor function and worsening of disability.
PXT3003 is designed to target the effect of the extra PMP22 gene copy and limit further progression of the disease

Study objective

Primary:
To evaluate the efficacy of treatment with PXT3003 (a fixed-dose combination of (RS)-baclofen, naltrexone hydrochloride, and D-sorbitol) compared to placebo in subjects with CMT1A.

Secondary:
To evaluate the safety and tolerability of PXT3003 treatment in subjects with CMT1A.

Study design

Randomized, Double-blind, Placebo controlled intervention study

Intervention

One group will receive two stick-packs with PXT3003 twice daily and the second group will receive two stick-packs with placebo twice daily.

Study burden and risks

During the treatment period we will carry out these checks:
* Physical examination.
* Neurlogical examination. (Only at first visit of treatment period)
* General questions on how you feel and if you have any side effects. We will also check your current use of medication. (At each hospital visit and during the telephone calls)
* Blood collection. The investigator takes 1-4 tubes of blood at a time. During the study, we will collect 148 ml of blood from you. This amount does not cause any problems in adults. For comparison: if you give blood at the blood bank, you will give 500 ml of blood at a time. With the blood test, we test these things:
o Your general health
o What your body does to the study medication. For this we will take blood

before you take your dose of study medication in the hospital and 90 minutes after you took the study medication. (4x)
o What the study medication does to your body.
* Urine test. This is done to test your general health (3x) and if applicable, to test for pregnancy (3x).
* Nerve conduction test (4x).
* Heart ultrasound.
* Questionnaires. We will ask you to complete several questionnaires on your mental and physical health.
* Walking test. You will be asked to do a 10 meter walking test.
* Strength measurements. Your hand and foot strength will be measured (4x).

The possible side effects that you could experience when having treatment with PXT3003 could include:
* Nausea
* Indigestion
* Diarrhea
* Constipation
* Stomach pain
* Dry mouth
* A cold
* Headache
* Fatigue
* Weakness
* Sleepiness or inability to sleep
* Dizziness
* Ringing in the ears
* Joint/muscle pain
* Muscle spasm

Allergic Reactions
As with taking any medication, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of an allergic reactions are: shortness of breath, itchy rash (hives) or swelling, flushing (feeling warm), low blood pressure, and slow heart rate. You should get medical help and contact the study doctor or staff if you have any of these or any other side effects during the study.

Blood Sampling
To take blood from you, a needle will be inserted into your vein. The risks of taking blood include fainting and pain, bruising, swelling, or rarely, infection where the needle was inserted. The total amount of blood to be collected during your participation in this research study will be approximately 148 mL. This does not include possible additional blood that may be collected during unscheduled visits or tests.

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

Nerve conduction test
To assess how well your nerves are relaying electrical messages, sticky electrodes which can detect electrical signals will be placed on the skin. De nerve will then be stimulated with little electric shocks on different places. This can be experienced as painful during the test.

Risks to an Unborn Child
This study can have consequences for an unborn child. The consequences are not known. The investigator will tell you how best to prevent pregnancy. Talk to your partner about this.
If you are exclusively in a same-sex sexual relationship, you are not required to use a method of contraception for this study as listed below.

Contacts

Public
Pharnext SA

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FR
Scientific
Pharnext SA

rue Saint Lazare 46
Paris 75009
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

1. Male and non-pregnant female subjects, aged 16 to 65 years with a genetically proven diagnosis of CMT1A.
2. Able to provide written informed consent/assent and comply with study procedures.
3. Mild-to-moderate severity assessed by a CMTNS-V2 score >2 and *18.
4. Muscle weakness in at least foot dorsiflexion on clinical assessment.
5. Ulnar nerve motor conduction time of at least 15 m/s.
6. If taking prescribed psychoactive drug(s) (eg, antidepressants, stimulants, tranquilizers, anti-epileptics) for CMT1A, should be on a stable dose for at least 4 weeks prior to randomization, which is not planned to be changed.
7. If taking prescribed or *over-the-counter* analgesic medication(s) (eg, paracetamol/acetaminophen, nonsteroidal anti-inflammatory drugs) for CMT1A, should be on a stable dose for at least 2 weeks prior to randomization, which is not planned to be changed.
8. If female, subject must be: (a) surgically sterilized via hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; or (b) of childbearing potential and using a birth control method such as:
* Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
o Oral
o Intravaginal
o Transdermal
* Progestogen-only hormonal contraception associated with inhibition of ovulation:
o Oral
o Injectable
o Implantable
* Intrauterine device
* Intrauterine hormone-releasing system
* Bilateral tubal occlusion
* Vasectomized partner
* Sexual abstinence
or (c) Of non-childbearing potential (ie, no menses for *12 consecutive months without any other underlying medical cause)
9. If male, the subject must have had a vasectomy or must use a reliable method of birth control with their partner or total abstinence from sexual intercourse. The subject must agree to continue using their selected method of birth control with their sexual partner during the study and for 120 days after study completion.

Exclusion criteria

1. Subjects previously enrolled in any PXT3003 study.
2. Subjects living in the same household and enrolled in a PXT3003 study (due to potential lack of adequate storage for study material, risk of mixing treatments and potential unblinding).
3. CMT of any subtype other than 1A.
4. ONLS score of 0.
5. Known clinically significant motor or sensory abnormalities secondary to a different neurological cause (eg, diabetes, alcohol, vascular, autoimmune, neoplastic, neurodegenerative, human immunodeficiency virus, etc.). Note: subjects with diagnosis of unilateral carpal tunnel syndrome at least 1 year prior to Screening Visit, that is asymptomatic at the time of Screening Visit, will not be excluded from participating in this study.
6. Subjects who have had any surgery or have a concomitant disorder (eg, severe arthrosis) that reduces the mobility of the ankle or wrist making it, in the opinion of the investigator, difficult to assess the efficacy of the treatment. Note: subjects with surgical repair of unilateral carpal tunnel syndrome will not be excluded from participating in this study.
7. Known peripheral neuropathy, myopathy, or neuromuscular disorder of any other kind. Note: subjects with diagnosis of unilateral carpal tunnel syndrome at least 1 year prior to Screening Visit, that is asymptomatic at the time of Screening Visit, will not be excluded from participating in this study.
8. Any other clinically significant and/or uncontrolled medical condition that, in the opinion of the investigator, could be a confound, may increase subject*s risk, or may preclude successful participation or completion of the study.
9. Known hypersensitivity or intolerance to PXT3003 (or matching placebo), including any of its active ingredients (baclofen, naltrexone, or sorbitol), and/or any of its excipients (acetate buffer, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, or isoamyl acetate).
10. Concomitant treatments including but not limited to baclofen, naltrexone, sorbitol (pharmaceutical form), opioids, potent central nervous system depressants (such as barbiturates, long-acting benzodiazepines, and neuroleptics), and potentially neurotoxic drugs such as amiodarone, chloroquine, and chemotherapeutics capable of inducing peripheral neuropathy. Subjects able to stop these medications at least 2 weeks before randomization and for the study duration may be included. Subjects with positive urine drug screen at Baseline Visit will be excluded, except for permitted use of codeine and benzodiazepines (see Appendix 2 from the protocol: List of Prohibited Treatments).
11. History of porphyria.
12. Diagnosis or history of substance use disorder by Diagnostic and Statistical Manual of Mental Disorders-5th Edition criteria within the past 12 months.
13. Medical or recreational use of marijuana in the 3 months prior to the Screening Visit.

14. Active suicidality (eg, any suicide attempts within the past 12 months or any current suicidal intent, including a plan, as assessed by the C SSRS score of *YES* on questions 4 or 5; and/or based on clinical evaluation by the investigator).
15. Currently active major depression, as determined by a Beck Depression Inventory-II (BDI-II) score *20.
16. Currently lactating, pregnant, or planning on becoming pregnant during the study.
17. Alanine aminotransferase or aspartate aminotransferase levels greater than 2 times the upper limit of normal.
18. Significant renal impairment as determined by glomerular filtration rate of less than 50 mL/min.
19. Subject has participated in an investigational drug or device study within 30 days prior to the Screening Visit or plans to participate in an investigational drug or device study during the course of this study.
20. Subject is a dependent and/or relative of the Sponsor or Principal Investigator.

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:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	PXT3003
Generic name:	PXT3003

Ethics review

Approved WMO Date:	27-05-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2020-004805-30-NL
ClinicalTrials.gov	NCT04762758
CCMO	NL76740.018.21