Old Title: International, multi-center, open label 9-month FOLLOW-UP extension study assessing the long term safety and tolerability of PXT3003 in patients with Charcot-Marie-Tooth Disease type 1A.;New title : International, multi-center, open label FOLLOW-UP extension study assessing the long term safety and tolerability of PXT3003 in patients with Charcot-Marie-Tooth Disease type 1A.

Published: 28-03-2017
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The primary objectives:Period 1:The primary objective is to assess the long-term (up to 2 years) safety and tolerability of two doses of PXT3003.Period 2:For patients continuing after V9, the main objective will be to offer patients the opportunity...

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

Summary

ID

NL-OMON53119

Source
ToetsingOnline

Brief title
PLEO-CMT follow-up (CLN-PXT3003-03)

Condition

- Neurological disorders congenital
- Peripheral neuropathies

Synonym
HMSN hereditary motor and sensory neuropathy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Charcot MarieTooth disease type 1A, disorder of peripheral nervous system, neurological disorder, progressive loss of muscle tissue

Outcome measures

Primary outcome

Period 1:

To assess the safety and tolerability of PXT3003 in CMT1A patients during a

long term period, the primary endpoint will be the incidence of

Treatment-Emergent Adverse Events (TEAEs) Related to the Investigational

Product during the follow-up, in patients to PXT3003 for up to 24 months or 9

months.

The incidence of TEAEs in the two groups P / D1-9m and P/ D2-9m will be

compared to the first 9-month placebo period in the primary study.

The incidence of TEAEs in the two groups D1-24m, D2-24m will be compared to the

first 9-month period in the primary study for their corresponding group

Period 2:

After V9, the incidence of TEAEs related to investigational product will be described.

Secondary outcome

Period 1:

Safety:

- Incidence of all TEAEs and their evaluation of type/nature, severity/intensity, seriousness, duration, relationship to study drug, and outcome;
- Incidence of AE leading to withdrawal of study drug;
- Changes in laboratory parameters, ECGs, vital signs and physical examinations;

The clinical response will be assessed by the change over time of the following efficacy endpoints:

- the Overall Neuropathy Limitation Scale (ONLS) score, and its arm and leg sub-items;
- the Charcot-Marie-Tooth Neuropathy Score - version 2 (CMTNS-V2), and its subitems;
- the functional assessments measured by Nine-hole Peg Test (9-HPT), Quantified
- Muscular Testing (QMT) by hand grip and foot dorsiflexion dynamometry (mean of both sides), and Time to walk 10 meters;
- electrophysiological parameters assessing sensory and motor responses of ulnar and radial nerves (non-dominant side) including Compound Muscle Action Potential (CMAP) on ulnar nerve; Sensory Nerve Action Potential (SNAP) on radial nerve; and Nerve conduction velocity (NCV);

- the EuroQol 5-Dimensional Health-related Quality of Life scale (EQ-5D);

- the individualized main impairment in daily activities (defined at baseline with the patient) by self-assessment on visual analog scale.

For the patients receiving up to 24 months of active dose along the two successive studies (from groups D1-24m and D2-24m) the clinical response will be assessed by the change from Visit 1/baseline of each endpoint.

For the patients who received placebo during the 15-month primary study and active drug during the 9-month extension study (from groups P/D1-9m and P/D2-9m) the clinical response will be assessed after 9 months of PXT3003 treatment by the change from Visit 6/baseline.

The Percentage of responders to PXT3003 defined as a patients improving on ONLS at end of treatment (Visit 9) will be assessed in the patients receiving the active dose of PXT3003 during up to 24 months (from groups D1-24m, D2-24m).

Period 2

After V9,

- the incidence of all TEAEs and their evaluation of type/nature, severity/intensity, seriousness, duration, relationship to study drug, and outcome;

- the incidence of AE leading to withdrawal of study drug will be described.

After V9, the Overall Neuropathy Limitation Scale (ONLS) score, and its arm and leg sub-items shall be assessed every 6 months and the clinical response will be assessed by the change over time of ONLS. With the ONLS the arm and muscle

function is measured.

Study description

Background summary

CMT1A, the most frequent CMT subtype (40 to 50% of all CMT), belongs to the group of inherited, progressive, chronic sensory and motor peripheral neuropathies referred to as Charcot-Marie-Tooth (CMT) disease or also as *Hereditary Motor and Sensory Neuropathy* (HMSN) or *Peroneal Muscular Atrophy* (PMA). CMT1A is caused by a specific duplication in the gene encoding for the "peripheral myelin protein of 22 Kilodalton" (PMP22). It isexpressed in Schwann cells and could be defined as a gene-dosage disease causing a 1.5-fold over-expression of the PMP22 protein in Schwann cells. The moderately elevated expression of this gene disrupts peripheral nerve myelination by Schwann cells and consecutively, slows signal transmission alongside the axons and deprives them of important neurotrophic factors normally provided by mature Schwann cells. Ultimately, axonal loss is responsible for the clinical phenotype due to muscle and sensory organ denervation. PXT3003, is a fixed dose combination of (RS)-baclofen, naltrexone hydrochloride and Dsorbitol selected via a Systems Biology approach and developed by Pharnext, with the aim to lower toxic PMP22 gene over-expression in CMT1A.

Study objective

The primary objectives:
Period 1:
The primary objective is to assess the long-term (up to 2 years) safety and tolerability of two doses of PXT3003.
Period 2:
For patients continuing after V9, the main objective will be to offer patients the opportunity to access to twice Dose 1 equivalent to Dose 2 of PXT3003, with a regular safety follow-up

The secondary objectives are:
Period 1:
- To gather long-term data (up to 2 years) to assess and estimate the long-term effect of PXT3003 on clinical, functional and electrophysiological endpoints;
- To compare the effect of PXT3003 in patients receiving PXT3003 active dose from the start of the primary study versus patients assigned to a delayed start (i.e., who received placebo during the primary study) in order to show if PXT3003 slows the progression of the disease, as measured via clinical scores;
- To assess the evolution of potential blood biomarkers and molecular changes

in skin biopsy on longer term.
Period 2:
For patients continuing after V9, sefty follow-up and ONLS score follow-up on a 6-month frequency.

Study design

Period 1 : International, multi-center open-label, study testing two doses of PXT3003 during 9 months, following the up to 15-month primary study (CLN-PXT3003-02).

Period 2 : International, multi-center, open-label study offering access to twice Dose 1 equivalent to Dose 2 of PXT3003 until the first marketing authorization is obtained (estimated in 2024).

Intervention

Period 1:
PXT3003 is a fixed dose combination of RS-baclofen, naltrexone hydrochloride and Dsorbitol.
Two active doses will be tested:
Dose 1 = 3 mg baclofen, 0.35 mg naltrexone and 105 mg sorbitol given per oral route twice daily; 5 ml per intake
Dose 2 = 6 mg baclofen, 0.70 mg naltrexone and 210 mg sorbitol given per oral route twice daily; 10 ml per intake.
Investigational treatments will be supplied as 100 mL clear oral solution in amber glass bottle (for 10 days of treatment); they will be provided in carton boxes of 4 bottles. Since this is a double blind study, both doses will be provided with the same presentation and taste.
Bottle will be delivered with a plastic adapter and an adaptable plastic pipette for medication dispensation. The pipette will have 2.5-mL and 5-mL graduations, corresponding to half-dose and full dose of the medication to be administered twice daily (morning and evening with food).

To improve treatment tolerability, all the patients will take the half-dose during the first two weeks before the full dose during the rest of the 9 months.
Patients in dose 1 will take 2.5 mL, twice daily in first 2 weeks and thereafter 5 mL, twice daily. Patients in dose 2 will take 5 mL, twice daily in first 2 weeks and thereafter 10 mL (2x5), twice daily.

Period 2:
After V9, only twice dose 1 equivalent to dose 2 of PXT3003 will be used:
D2 = equivalent to twice D1 (6 mg baclofen, 0.70 mg naltrexone and 210 mg sorbitol) given per oral route (10 mL total volume, i.e. twice 5 mL) twice daily.

Study burden and risks

The study includes administration of the study drug twice daily during 9 month. As with all drugs, the patients may experience adverse events, as described in section E9, although PXT3003 showed good tolerance. Patients will undergo other examinations like blood samples,10 min walking test, ECG, electromyogram. Some discomfort may result of these tests. This is also described in section E9 of this form. Patients who are taking the study drug (group dose 1 and 2) may have an improvement of the disease.

Contacts

Public
Pharnext SA

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Period 1:

- Patients must have completed 15 months of double-blind treatment in the primary study CLN-PXT3003-02, including all procedures required at the Study Termination visit (V6) or patients under D2 prematurely discontinued from CLN-PXT3003-02 (due to sponsor decision on September 18th, 2017) must have performed an early V6.
- Patients must have completed the V6 assessments within the 4 weeks prior to extension study or patients who have completed a new baseline visit (VB) if the V6 assessments were not completed in the 4 weeks prior to study entry.
- Female patients must agree to continue using an approved method of birth control throughout the extension study.
- Patients must sign a written informed consent, specific to the extension study, in order to participate in this study. In case of minor patients were included in the primary study, they will need to have reached their majority, so only adult patients will be included in the extension study.
Period 2:
Patients must sign a written informed consent to continue after V9 to access to study treatment.

Exclusion criteria

- Any clinically significant change in health status that, in the opinion of the Investigator, would prevent the subject from participating in this study or successfully completing this study.
- Any unauthorized concomitant treatments, in the 4 weeks preceding study entry, as study CLN-PXT3003-02 .

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	30-01-2018
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PXT3003
Generic name:	PXT3003

Ethics review

Approved WMO Date:	28-03-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	24-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	29-11-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	21-05-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	13-09-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.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
EudraCT	EUCTR2015-002379-81-NL
CCMO	NL60471.018.17