International, multi-center, randomized, double-blind, placebo-controlled phase III study assessing in parallel groups the efficacy and safety of 2 doses of PXT3003 in patients with Charcot-Marie-Tooth Disease type 1A treated 15 months

Published: 17-12-2015
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Primary objective:To assess the efficacy of PXT3003 compared to Placebo on the disability measured by the ONLS score in CMT1A patients treated for 15 months.Secondary objectives:- To assess the efficacy of PXT3003 compared to Placebo on clinical and...

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

Summary

ID

NL-OMON46863

Source
ToetsingOnline

Brief title
CLN-PXP3003-02

Condition

- Neurological disorders congenital
- Peripheral neuropathies

Synonym
HMSN hereditary motor and sensory neuropathie

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Charcot-Marie-Tooth type 1A, PXT3003

Outcome measures

Primary outcome

Improvement of disability measured by the Overall Neuropathy Limitation Scale

(ONLS)

score.

Secondary outcome

Responders Rate to PXT3003 therapy defined as a patients improving on ONLS at

end of

treatment;

- The effect of the studied PXT3003 dosages on the following endpoints:

* Arm and leg sub-items of ONLS;

* Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNS-v2), including its

subitems;

* Nine-hole Peg Test (9-HPT) performed on non-dominant hand;

* Quantified Muscular Testing (QMT) by Hand grip and Foot dorsiflexion

dynamometry (mean of both sides);

* Time to walk 10 meters;

* Electrophysiological parameters assessing sensory and motor responses of ulnar

and radial nerves (non-dominant side) including:

o Compound Muscle Action Potential (CMAP) on ulnar nerve;

o Sensory Nerve Action Potential (SNAP) on radial nerve;

o Nerve conduction velocity (NCV);

* Quality of life measured by:

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

o VAS on self-assessment of the individualized main impairment in daily

activities defined at baseline with the patient.

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) expressed 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. The expected effect of the combination of the three drugs in the treatment of CMT1A has been demonstrated first pre-clinically ex vivo and in vivo (Chumakov, Milet et al., 2014), and then by a phase II proof of concept study testing 3 doses of the combination at the same ratio compared to Placebo in 80 patients with CMT1A treated for 12 months. This phase II study demonstrated the good tolerability and safety of 3 tested doses of PXT3003 (primary outcome measure) and provided preliminary evidence of efficacy with a significant *doseeffect*

and an increasing effect among the 3 tested doses demonstrating positive results after 12 months on the selected relevant clinical and electrophysiological outcome measures only for the highest Dose. At this highest dose baclofen, naltrexone and sorbitol were administrated at much lower doses (10 to 100 times less) than used for their respective approved indications as daily doses were 6 mg baclofen, 0.7 mg naltrexone and 210 mg sorbitol (Attarian, Vallat et al., 2014).
It is postulated that PXT3003 deserves further clinical investigation in a pivotal confirmatory study in a larger CMT1A population. For this next study, 2 doses will be tested, compared to placebo: the highest dose found effective in the phase II and a higher dose (double dose with the same ratio between each active components of PXT3003). The choice for this additional dose was limited by the baclofen dosage, that could not be increased above 6 mg given twice a day, in order to avoid known side effects with this drug particularly for chronic administration in active young people, and to preserve a good safety profile. As there is no approved treatment in CMT1A, there is no comparator to introduce, as usually done in
Phase III trials. The 2 tested doses will be compared only to Placebo in a randomized double-blind design with 3 balanced groups (1:1:1).

Study objective

Primary objective:
To assess the efficacy of PXT3003 compared to Placebo on the disability measured by the ONLS score in CMT1A patients treated for 15 months.

Secondary objectives:
- To assess the efficacy of PXT3003 compared to Placebo on clinical and functional tests, electrophysiological parameters, and measures of quality of life;
- To assess the safety and tolerability of PXT3003 compared to Placebo;
- To assess plasma concentrations of PXT3003 components (at peak and trough) when administered with 2 different doses;
- To assess the change over time of potential blood biomarkers;
- To assess molecular changes in skin biopsy, when this procedure will be possible (ancillary sub-study);
- To explore potential new imaging biomarkers by calf MRI, when this procedure will be possible (ancillary sub-study).

Study design

Phase III, double-blind, international, multi-center randomized, placebo-controlled study with 3 parallel groups (PXT3003 Dose 1, PXT3003 Dose 2 or matching Placebo (1:1:1)), for 15 months (65 weeks).

Intervention

A total of 300 patients will be randomized (1:1:1) into 3 parallel groups :
Dose 1 = 3 mg baclofen, 0.35 mg naltrexone and 105 mg sorbitol given twice daily;
Dose 2 = 6 mg baclofen, 0.70 mg naltrexone and 210 mg sorbitol given twice daily;
The control group will be matching placebo.

The study drug (PXT3003 or matching placebo) will be administered per oral route 5 ml twice daily (morning and evening with food) for 15 months.

Study burden and risks

The study includes administration of the study drug twice daily during 15 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. All patients will be proposed to participate to an extension study where they will be given the active product.

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

1. Male or female, aged from 16 to 65 years;
2. Patient with a proven genetic diagnosis of CMT1A;
3. Mild-to-moderate severity assessed by CMTNS-v2 with a score >2 and *18;
4. Muscle weakness in at least foot dorsiflexion (clinical assessment);
5. Motor nerve conduction of the ulnar nerve of at least 15m/sec;
6. Providing signed written informed consent to participate in the study and willing and able to comply with all study procedures and scheduled visits.

Exclusion criteria

1. Any other associated cause of peripheral neuropathy such as diabetes;
2. Patients with another significant neurological disease or a concomitant major systemic disease;
3. Clinically significant history of unstable medical illness since the last 30 days (unstable angina, cancer*) that may jeopardize the participation in the study;
4. Significant hematologic disease, hepatitis or liver failure, renal failure;
5. Limb surgery within six months before randomization or planned before trial completion;
6. Clinically significant abnormalities on the pre-study laboratory evaluation, physical evaluation, electrocardiogram (ECG);
7. Elevated ASAT/ALAT (> 3 x ULN) and elevated serum creatinine levels (> 1.25 x ULN);
8. History of recent alcohol or drug abuse or non-adherence with treatment or other experimental protocols;
9. Patients using unauthorized concomitant treatments including but not limited to baclofen, naltrexone, sorbitol (pharmaceutical form), opioids, levothyroxin and potentially neurotoxic drugs such as amiodarone, chloroquine, cancer drugs susceptible to induce a peripheral neuropathy; (list provided in appendix 1). Patients who can/agree to stop these medications 4 weeks before randomization and during the whole study duration can be included;
10. Female of childbearing potential (apart of patients using adequate contraceptive measures), pregnant or breast feeding;

11. Known hypersensitivity to any of the individual components of PXT3003;
12. Porphyria as it is a contra indication to baclofen, and it may also induce neuropathy;
13. Suspected inability to complete the study follow-up (foreign workers, transient visitors, tourists or any others for whom follow-up evaluation is not assured);
14. Limited mental capacity or psychiatric disease rendering the subject unable to provide written informed consent or comply with evaluation procedures;
15. Patients who have participated in another trial of investigational drug(s) within the past 30 days;
16. If a patient from the same family, living in the same household, has already been included in this study, it will not be possible to include another patient from the same family to avoid mixing of therapeutic units; therefore there would be a risk of inversion of the blind treatments which could jeopardize the interpretation of study results.

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:	Recruitment stopped
Start date (anticipated):	23-08-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	17-12-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2017
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:	16-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2018
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	EUCTR2015-002378-19-NL
ClinicalTrials.gov	NCT02579759
CCMO	NL55281.018.15