PROTOCOL CLN-PXT3003- 02

STUDY PLEO-CMT (PLEO-CHARCOT MARIE TOOTH)

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

EUDRACT N° 2015-002378-19

IND N° 122505

Protocol version: N° 1.4 dated December 05th 2017

Investigational drug: PXT3003
a fixed dose combination of RS-Baclofen, Naltrexone hydrochloride and D-Sorbitol

Sponsor: **PHARNEXT**
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PROTOCOL VERSION HISTORY

Version	Date	Revision Summary
V1.0	22MAY15	Final version
V1.1	01SEP15	Interim Analysis added
V1.2	16FEB2016	1- Calf MRI changes in leg MRI 2- Added possibility to perform the PMP22 duplication genetic test if not already documented in patient history
V1.3	18JAN2017	1- removal of Synteract CRO name on the cover page + correction of a typo error in the section 13.1, 2nd§: written 6β-naltrexol instead of 6β-naltrexone. 2- the wording of "a total of 300 patients" is replaced by a "total of at least 300 patients" to cover the fact that a total of 323 patients were actually randomized in the study. Due to the high number of screened patients, it was deemed appropriate to keep screened and eligible patients to participate in the study. This adaptation is applied in the following sections: Synopsis (in the 2 sub-sections "total expected number of patients" and "Statistical considerations") and in 8.3, 9, 14.3.
V1.4	05DEC2017	Rationale for moving from V1.4 to V1.5: due to an unexpected investigational medicinal product (IMP) quality event, without safety concerns, the use of dose 2 IMP is discontinued from the pivotal phase III study CLN-PXT3003-02 upon Sponsor decision (September 18th, 2017). The stability testing at Quay Pharma (UK) observed the occurrence of crystals in one stability batch of PXT3003 dose 2 at month 18 (September 14th, 2017), whereas this was not the case at month 12. This new finding is inconsistent with the dose 2 IMP release criteria and therefore does not meet the ICH Harmonized Tripartite Guideline for Stability Testing of New Drug Substances and Products. Hence, the patient arm of PXT3003 dose 2 will early terminate the study. They will be offered to enter the extension study CLN-PXT3003-03 to receive the equivalent of dose 2 (5 mL per administration), by using of its equivalent dose, i.e. twice the dose 1 IMP (2x5 mL, i.e. 10 mL) per administration. Furthermore, all patients using dose 1 IMP or placebo will continue to receive dose 1 IMP or placebo (5 mL per administration) in the pivotal phase III study CLN-PXT3003-02 as planned.

IMPACTED OF THE PROTOCOL AMENDMENT V1.4

1. How to manage the dose 2 patient group discontinuation?	The PXT3003 dose 2 study arm will discontinue prematurely from study CLN-PXT3003-02, in accordance with section 11.6.1 "if the study is prematurely discontinued then enrolled patients should be called for an end of study visit". Hence, there is no need to implement additional information in the protocol. The sites will receive additional useful instructions to organise the recall of dose 2 IMP patients.
2 Statistical sections: how to manage incomplete data	Due to incomplete data in the dose 2 arm, the missing data will be evaluated as described in the section 14.5 of the protocol.
3 Section 11.7 follow up extension study – adapted as followed	Patients who completed this 15-month study or who were prematurely discontinued from the PXT3003 dose 2 administration will be offered to enter the open-label extension study CLN-PXT3003-03. Patients previously assigned to dose 2 PXT3003 will receive the equivalent of dose 2 (i.e. 5 mL per administration), by use of its equivalent dose, i.e. twice the dose 1 PXT3003 (2x5 mL, i.e. 10 mL per administration) in the study CLN-PXT3003-03. Patients previously assigned to dose 1 PXT3003 or placebo and who have completed the pivotal phase III study will receive dose 1 PXT3003 (5 mL) in the study CLN-PXT3003-03. Hence the protocol of extension study has been amended to assign all placebo patients to dose 1 IMP only, whereas patients previously assigned to dose 1 IMP will continue to do so. As a consequence of the difference of IMP volume (i.e. 5 mL and 10 mL) to be administered the study has become an open-label study that no longer randomizes patients to study treatment.

Signature page for sponsor representative

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The study will be conducted in compliance with the following protocol and will be carried out in accordance with Good Clinical Practice (GCP) as required by the ICH GCP E6 and local applicable regulatory requirements in the participating countries.

Rationale for moving from V1.3 to V1.4: due to an unexpected investigational medicinal product (IMP) quality event, without safety concerns, the use of dose 2 IMP is discontinued from the pivotal phase III study CLN-PXT3003-02 upon Sponsor decision (September 18th, 2017).

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Furthermore, all patients using dose 1 IMP or placebo will continue to receive dose 1 IMP or placebo (5 mL per administration) in the pivotal phase III study CLN-PXT3003-02 as planned.

I fully agree to the contents of this protocol which gives all the necessary information to conduct this study.

Name: **René GOEDKOOP**
Chief Medical Officer

Date: December 8th, 2017

Signature:

Signature page for coordinating investigator

PROTOCOL CLN-PXT3003- 02

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I fully agree to the contents of this protocol which gives all the necessary information to conduct this study. I hereby accept to coordinate this study:

The coordinator in ……. Date : _____

Name: ……

Hospital: …… Signature: _____

Address: ……

Signature Page for Investigators

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*The signature below constitutes the approval of this **protocol CLN-PXT3003-02** and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all the statements regarding confidentiality, and according to local legal and GCP regulatory requirements and ICH guidelines.*

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I fully agree to the contents of this protocol which gives all the necessary information to conduct this study. I hereby accept to coordinate this study:

The site investigator …….. Date : _____

Name: ……

Hospital: …… Signature: _____

Address: ……

Summary of Changes
From V1.3 to V1.4

N° Changes Page / section	V1.3 (Initial text)	V1.4 (Text modified)
Each page (heading)	Protocol CLN-PXT3003-02, Version 1.3	Protocol CLN-PXT3003-02, **Version 1.4**
Pages: 1-4-5-6	Protocol version: N° 1.3 and rationale moving from V1.3 to V1.4	Protocol version **N°1.4** Rationale for moving from V1.3 to V1.4: due to an unexpected investigational medicinal product (IMP) quality event, without safety concerns, the use of dose 2 IMP is discontinued from the pivotal phase III study CLN-PXT3003-02 upon Sponsor decision (September 18th, 2017). The stability testing at Quay Pharma (UK) observed the occurrence of crystals in one stability batch of PXT3003 dose 2 at month 18 (September 14th, 2017), whereas this was not the case at month 12. This new finding is inconsistent with the dose 2 IMP release criteria and therefore does not meet the ICH Harmonized Tripartite Guideline for Stability Testing of New Drug Substances and Products. Hence, the patient arm of PXT3003 dose 2 will early terminate the study. They will be offered to enter the extension study CLN-PXT3003-03 to receive the equivalent of dose 2 (5 mL per administration), by using of its equivalent dose, i.e. twice the dose 1 IMP (2x5 mL, i.e. 10 mL) per administration. Furthermore, all patients using dose 1 IMP or placebo will continue to receive dose 1 IMP or placebo (5 mL per administration) in the pivotal phase III study CLN-PXT3003-02 as planned.
Synopsis **Planned dates**	NA	Last patient out (ie., end of study): expected Q12018 in all the countries, except in Germany where the LPO is expected Q3 2018* Clinical Study Report: expected Q2 2019, * due to longer interruption of the study in Germany regarding the occurrence of crystals in the dose 2 IMP, the LPO in Germany is expected in Q3 2018

Section 11.2.7 Bullet 8	Blood samples for PK (one before dosing, and one 90 minutes after drug intake)	Blood samples for PK (one before dosing, and one 90 minutes after drug intake) o Attention: PK samples are not applicable in the dose 2 arm if the end of study visit is performed due to discontinuation of the dose 2 arm
Section 11.7 Follow up extension study	NA	From V1.4: Patients who completed this 15-month study or who were prematurely discontinued from the PXT3003 dose 2 administration will be offered to enter the open-label extension study CLN-PXT3003-03. Patients previously assigned to dose 2 PXT3003 will receive the equivalent of dose 2 (i.e. 5 mL per administration), by use of its equivalent dose, i.e. twice the dose 1 PXT3003 (2x5 mL, i.e. 10 mL per administration) in the study CLN-PXT3003-03. Patients previously assigned to dose 1 PXT3003 or placebo and who have completed the pivotal phase III study will receive dose 1 PXT3003 (5 mL) in the study CLN-PXT3003-03. Hence the protocol of extension study has been amended to assign all placebo patients to dose 1 IMP only, whereas patients previously assigned to dose 1 IMP will continue to do so. As a consequence of the difference of IMP volume (i.e. 5 mL and 10 mL) to be administered the study has become an open-label study that no longer randomizes patients to study treatment.

1. SYNOPSIS

Study No:	CLN-PXT3003-02 **Study name:** PLEO-CMT
Title	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 for 15 months.
Phase	Phase III
Indication	Charcot Marie Tooth Disease - Type 1A (CMT1A)
Investigational Drug	PXT3003, a fixed dose combination of RS-Baclofen, Naltrexone hydrochloride and D-Sorbitol
Study Design	Double-blind, randomized, placebo-controlled, 3 parallel groups, international multi-center study for 15 months (65 weeks).
Study duration	Patients will be randomized after a screening period (up to 30 days) during which selection criteria are verified and baseline assessments such as electrophysiological testing, lab tests and ECG are performed. Then, after randomization, patients will be included in the study under double blind study medication for 15 months.
Total expected number of patients	A total of at least **300 patients** will be randomized (1:1:1) into 3 parallel groups: PXT3003 Dose 1, PXT3003 Dose 2 or matching Placebo (100/group), to achieve a power of at least 90% to detect the expected effect as significant with the primary efficacy analysis.
Rational	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 D-sorbitol 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 ‘dose-effect’ 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

Rational (con't)	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(s)	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 leg MRI, when this procedure will be possible (ancillary sub-study).
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

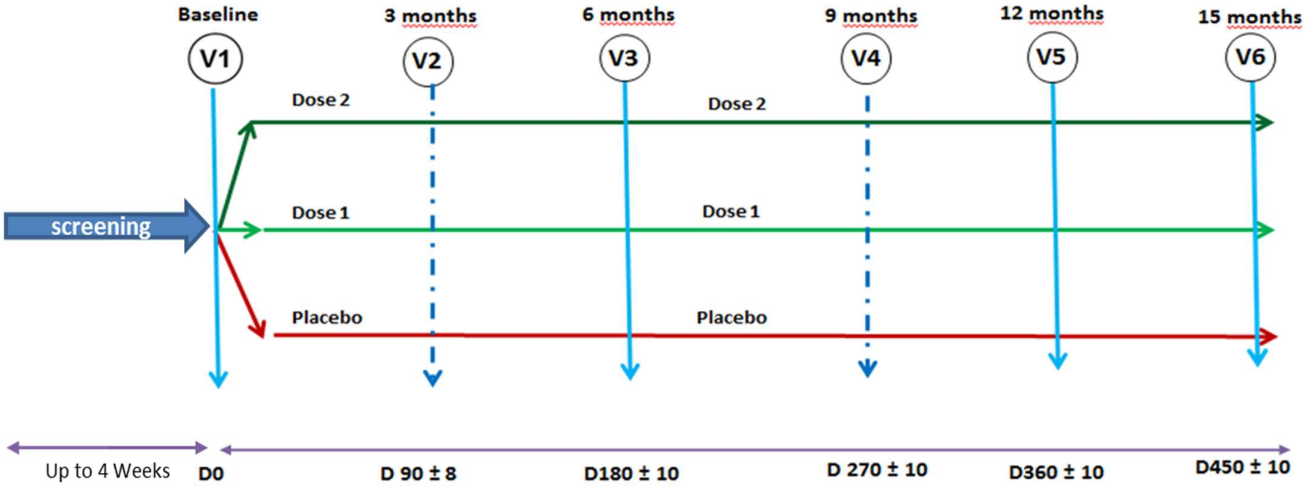
Exclusion criteria (con't)	experimental protocols; 9. Patients using unauthorized concomitant treatments including but not limited to baclofen, naltrexone, sorbitol (pharmaceutical form), opioids, levothyroxin and potentially neurotoxic drugs such as amiodarone, chloroquine, cancer drugs susceptible 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.
Investigational treatments **Dose regimen**	PXT3003 is a fixed dose combination of RS-baclofen, naltrexone hydrochloride and D-sorbitol. Two doses of PXT3003 will be tested: 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. Patients will be randomized in 3 groups in order to receive either PXT3003 at one of the 2 different doses or placebo. PXT3003 and placebo will be supplied as 100 mL clear oral solution in amber glass bottle (for 10 days of treatment) which will be delivered with a plastic adapter and an adaptable plastic pipette for medication dispensation which will be graduated with a 5 ml graduation corresponding to the full dose and 2.5 mL for the half-dose of medication to be administered. Each strength of PXT3003 corresponding to one of the tested dose levels and the placebo will have the same presentation and taste. PXT3003 and placebo will be provided in carton boxes of 4 bottles. 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. To improve tolerability, treatment should start progressively (for all randomized patients): half dose (2.5 mL of the liquid formulation) will be administered twice a day during the two first weeks and then will be increased to the full dose (5 mL of the liquid formulation) twice a day until the end of study treatment.
Concomitant treatments	Authorized treatments: Standard care for CMT1A, particularly occupational and physical therapy or drugs for pain (excluding opioids and benzodiazepines) are authorized and should be reported in the CRF; Prohibited treatments: - High doses of Ascorbic acid (≥1 g/day) - Levothyroxine;

Concomitant treatments (con't)	- Baclofen, naltrexone, and sorbitol in their current pharmaceutical forms at full dose. The use of opiates, and potentially neurotoxic drugs should also be avoided. A list of non-recommended treatments is provided in protocol section 21.
Primary efficacy endpoint	Improvement of disability measured by the Overall Neuropathy Limitation Scale (ONLS) score.
Secondary efficacy endpoints	- 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 sub-items; ▪ 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.
Secondary safety endpoints	Safety and tolerability of PXT3003 will be compared to placebo on the following parameters: - Incidence of all Treatment Emergent Adverse Events (TEAEs); they will be evaluated by type/nature, severity/intensity, seriousness, duration, relationship to study drug, and outcome; - Incidence of related TEAEs (including possibly and probably related TEAEs) with a moderate or severe intensity; - Incidence of AE leading to withdrawal of study drug; - Incidence of Serious Adverse Events (SAEs); - Change in physical examination, vital signs (blood pressure and heart rate), 12-lead ECG, and laboratory data (hematology and blood chemistry).
Additional exploratory endpoints	▪ <u>Plasma concentrations of baclofen, naltrexone and 6ß-naltrexol</u> will be obtained at Baseline, 6-months, 12-month and 15-month visits (PK samples at trough and at peak). ▪ <u>Blood biomarkers</u>: blood sampling will be performed for biomarkers and the tubes will be stored at -80°C o Pharnext has identified potential blood biomarkers in the previous phase II that need to be confirmed in this phase III: tryptophan, alanine, serotonin, T4, free cholesterol. Other markers could be assessed for quantification studies, and thus identified later after the accomplishment of this clinical trial. o Gene expression studies (microarrays and PCRs) may be also performed aiming to identify genes that could change in response to PXT3003 treatment, which could confer them the property of pharmacodynamics candidates. o DNA sequencing to advance the understanding CMT1A disease for the research

Additional exploratory endpoints (con't)	community in general for research purposes. ▪ Skin biopsy (*optional ancillary sub-study*) for molecular biology will be done (fixation for RNA preservation during 24 hours and then storage at -80°C until pick-up). Analysis RNA will be performed by Pharnext. ▪ MRI measure of muscle/fat index in the leg (*optional ancillary sub-study*), by MRI quantification of lower limb muscles and fatty muscle infiltration with centralized reading.
Statistical considerations	*Analysis populations:* The **Full Analysis Set (FAS)** will be constituted by all the randomized patients. The **Per-Protocol (PP)** population will include all the patients of the FAS without major protocol violation during the course of the study. All the efficacy analyses will be conducted on the FAS population and reproduced on the PP population for sensitivity purposes. The safety analyses will be conducted on the FAS, given that all randomized patients will receive at least one dose of treatment. *Primary efficacy analysis:* The significance of the studied drug effect compared with Placebo will be tested by an Analysis of Covariance (ANCOVA) on the summary mean of ONLS at 12 and 15 months adjusted for baseline ONLS values. ANCOVA will be featured by a Linear Mixed Model (LMM), including baseline ONLS values and treatment as fixed factors, and center as random effect. Two active doses will be compared to Placebo. As the monotonicity of dose effect is not assumed, each dose will be compared at a two-sided 2.5% significance level, in order to preserve an overall false-positive rate of 5%. *Sample size calculation:* Assuming ANCOVA with 2 post-baseline measures, a linear correlation coefficient of ONLS of R = 0.75 between baseline and end of the study, a standard deviation of ONLS of SD ≅ 1, a standardized mean difference of SMD = 0.3 should be detected versus Placebo with a power of 90% at a two-sided 2.5% significance level when the sample size reaches at least 89 patients per group. Assuming a drop-out rate of ≅ 10%, **we anticipate recruiting 100 patients per group for a total of at least 300 patients**. *Secondary efficacy analyses:* The primary ANCOVA analysis based on the summary mean at 12 and 15 months will be repeated on the other quantitative efficacy endpoints (see above). The significance of the treatment effect on each quantitative endpoint will also be evaluated based on the difference compared to Placebo in change from baseline at each individual visit and in slope of progression over the duration of the study. The proportion of responders at 15 months will be assessed through a Generalized Linear Mixed Model (GLMM) featuring logistic regression, and admitting center as a random effect. *Missing data:* Missing values will be imputed using a linear model estimated on the Placebo group. The potential impact of missing data on the study's conclusions will be evaluated. *Safety analyses:* Safety and tolerability will be assessed by summarizing and analyzing adverse events (AEs), change in physical examination, vital signs, electrocardiogram (ECG) and laboratory data. *Data Safety Monitoring Board (DSMB):*An independent DSMB will regularly follow the progress of the clinical trial, monitor safety data and critical efficacy variables, and be consulted concerning the opportunity of modifying the sample size or terminate the trial for futility. *Adaptive sample size:* An estimation of the adjusted standard deviation (ASD) will be performed when 80 patients are available. In case where the absolute value of the difference between the observed ASD and the value used for initial sample size calculation

Statistical considerations (con't)	exceeds 0.1, the sample size will be recalculated. The adaptive sample size calculation will be organized blind to treatment and do not require any type-I adjustment. *Futility analysis*: A one-stage Futility stopping will be based on Conditional Power, probability to detect a significant result at the end of the study, given the results observed at an intermediate time. Conditional Power (CP) will be estimated through B-values and (Lan and Wittes, 1988; Lan and Zucker, 1993). This analysis will be carried out by a third party statistician when at least 100 patients are available, and futility threshold will be CP_{min}=0.10 involving a slight increase of type 2 error (β = 0.1/0.9 = 0.111-0.10 ≅ 0.01) (Proschan, 1999). This intermediate futility analysis does not require any type-I adjustment, this trial does not plan g rejection of the null hypothesis before its end. Further details will be described in the Statistical Analysis Plan (SAP) as appropriate.
Study schedule	Usually patients come to visit their specialist annually and many of them may live far from the reference center, so the number of visits is limited. The study will be conducted for a **total of 15 months** with evaluation visits at baseline (screening and/or randomization visit), at 6, 12 and 15 months. Intermediate visits are scheduled at 3 and 9 months for drug dispensation, checking safety (AEs) and treatment compliance. Eventually if local regulations allow that the dispensing of medication can be organized by shipping, these intermediate visits at 3 and 9 months may be made by phone call. Visits will be scheduled as following: ▪ V0 - Screening visit: Day-1 to Day -30 max ▪ V1 - Inclusion visit (Baseline): at Day 0 ▪ V2 - 3-month visit (or telephone call): at Day 90 ± 8 Days ▪ V3 - 6-month visit: at Day 180 ± 10 Days ▪ V4 - 9-month visit (or telephone Call): at Day 270 ± 10 Days ▪ V5 - 12-month visit: at Day 360 ± 10 Days ▪ V6 - 15-month visit: at Day 450 ± 10 Days If one visit date is changed (anticipated or delayed), the next visit should occur according to the original schedule
Extension study, a DB 9-month Follow-up	In order to stimulate the recruitment and motivate patients to be enrolled, patients having completed the 15-month study will be eligible to receive PXT3003 in a follow-up extension trial for 9 months if they are willing to continue the treatment. They will be attributed to active drug by a second randomization. This 9-month extension study will provide additional long-term data on safety and additional efficacy data that could provide some evidence of disease modifying effect.
Planned dates	- CTA & IND submission: from June 2015 - Start (First patient in): Q4 2015 - Patients recruitment: 1 year (end of recruitment: Q4 2016) - Study duration for each patient: 15-month double-blind period - Last patient out (ie., end of study): expected Q1 2018 in all the countries, except in Germany where the LPO is expected Q3 2018* - Clinical Study Report: expected Q2 2019 * due to longer interruption of the study in Germany regarding the occurrence of crystals in the dose 2 IMP, the LPO in Germany is expected in Q3 2018

2. STUDY DESIGN



From V1.4: the dose 2 arm is discontinued due to unexpected IMP quality event, the occurrence of crystals observed in the dose 2 IMP

3. FLOW CHART

	←Screening period→	←Treatment period→					
Visits	**V 0**	**V 1**	V2/☎	**V 3**	V4/☎	**V 5**	**V 6**
Month		**0**	**3-month**	**6-month**	**9-month**	**12-month**	**15-month**
Day	**-30 to -1**	**0**	**90 ± 8**	**180 ±10**	**270 ± 10**	**360 ± 10**	**450± 10**
Inclusion exclusion criteria	**X**	**X**					
Informed consent	**X**						
Demographic data & medical history	**X**						
Diagnosis history (DNA) & treatments	**X**						
Physical and neurological examination	**X**	**X**		**X**		**X**	**X**
Vital signs	**X**	**X**		**X**		**X**	**X**
Electrophysiology (nerve conduction studies)	**X**	**X***		**X**		**X**	**X**
CMTNS-v2	**X**	**X***		**X**		**X**	**X**
ONLS		**X**		**X**		**X**	**X**
9 Hole PEG		**X**		**X**		**X**	**X**
QMT (dorsiflexion & handgrip)		**X**		**X**		**X**	**X**
10 metres Walk Test		**X**		**X**		**X**	**X**
Euro QoL-5D		**X**		**X**		**X**	**X**
VAS / main impairment / disability		**X**		**X**		**X**	**X**
Review of concomitant treatments	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood samples for safety	**X**	**X***		**X**		**X**	**X**
Blood samples for PK		**X**		**X**		**X**	**X**
Blood samples for Biomarkers		**X**		**X**		**X**	**X**
ECG	**X**	**X***					**X**
Skin Biopsy (*optional ancillary sub-study*)		**X**					**X**
Leg MRI *(optional ancillary sub- study)*		**X**					**X**
Treatment allocation		**X**					
Treatment dispensation		**X**	**X**	**X**	**X**	**X**	
Review of adverse events		**X**	**X**	**X**	**X**	**X**	**X**
Review of compliance			**X**	**X**	**X**	**X**	**X**

***** Electrophysiological testing to assess CMTNS score, and blood sample and ECG for safety will not be re-assessed at randomization (Visit 1) if they were performed at screening (Visit 0) within the previous 14 days. If time between V0 and V1 is greater than 14 days they must be repeated at randomization to assess baseline.

4. TABLE OF CONTENTS

5. LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
ALT	ALanine amino Transferase
ANCOVA	ANalysis of COVAriance
AST	ASpartate amino Transferase
BID	Bis In Die
BMI	Body Mass Index
cAMP	cyclic Adenosine MonoPhosphate
CBC	Complete Blood Count
CGI	Clinical Global Impression
CHMP	Committee for Medicinal Products for Human use
cm	centimeter
CMAP	Compound Muscle Action Potential
CMT	Charcot-Marie-Tooth
CMT1A	Charcot-Marie-Tooth Disease type 1A
CMTES	Charcot-Marie-Tooth Examination Score
CMTNS	Charcot-Marie-Tooth Neuropathy Score
CNS	Central Nervous System
CRO	Contract Research Organization
D	Day
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DNA	DeoxyNucleic Acid
DRG	Dorsal Root Ganglia
ECG	ElectroCardioGram
E-CRF	Electronic-Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GABA	γ – AminoButyric Acid
GABA-B	metabotropic transmembrane receptor for GABA
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Model
GRAS	Generally Recognised As Safe
hCG	human Chorionic Gonadotrophin
HED	Human Equivalent Dose
HMSN	Hereditary Motor and Sensory Neuropathy

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ITT	Intention-To-Treat
IV	IntraVenous
IWRS	Interactive Web Randomisation System
LC-MS/MS	high performance Liquid Chromatography coupled with Mass Spectrometry
LMM	Linear Mixed Model
MedDRA	Medical Dictionary for Regulatory Activities
m/s	meters per second
mRNA	messenger RiboNucleic Acid
NCS	Nerve Conduction Studies
NCV	Nerve Conduction Velocity
NDA	New Drug Application
ng	nanogram
NIS	Neuropathy Impairment Score
NYHA	New York Hear Association
OD	Once a Day
ODSS	Overall Disability Sum Score
ONLS	Overall Neuropathy Limitation Scale
PK	PharmacoKinetic
PMP22	Peripheral Myelin Protein 22
PP	Per-Protocol
PV	PharmaVigilance
PXT3003	fixed dose combination of baclofen, naltrexone and D-sorbitol
QMT	Quantified Muscular Testing
RD	Recommended Dose
RT-QPCR	Reverse Transcription-Real-time Quantitative PCR (QPCR)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard deviation
Sec	Second
SEM	Standard Error of the Mean
SmPC	Summary of Product Characteristics
SNAP	Sensory Nerve Action Potential

SOPs	Standard Operating Procedures
TEAE	Treatment Emergent Adverse Event
TG	TransGenic
TID	Ter In Die
T4	Thyroxin 4
UK	United Kingdom
ULN	Upper Limit of Normal Value
US	United States
VAS	Visual Analogue Scale
W	Week
WOCBP	WOmen of child bearing potential
WT	Wild-Type
°C	Degree Celsius
%	percent
γGT	Gamma –Glutamyl Transferase
µg	Microgram
µM	Micromole
µV	Microvolt
6MWT	Six Minute Walking Test

6. INTRODUCTION

6. 1 Charcot Marie Tooth disease - Type 1A (CMT1A): Background

CMT1A is a rare disease belonging 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), presently incurable, and the most common inherited disorder of the peripheral nervous system (PNS) (Kochanski, 2005; Patzko and Shy, 2011).

Different types of CMT disease can be distinguished by the types of lesions that disrupt nerve function and more recently, by the genetic causes. Although the neurophysiological classification remains the most widely used (CMT1 corresponding to the demyelinating type and CMT2 corresponding to the axonal type, as identified by median motor nerve conduction velocity studies), the more precise genetic classification is increasingly applied.

CMT1A is characterized by homogeneous and diffuse nerve conduction velocity (NCV) slowings (by definition: NCV) < 38 m/sec) which correspond to an homogeneous dysmyelination process, later followed by an axonal loss. CMT clinical phenotypes present common characteristics of progressive distal muscle weakness and atrophy, foot deformities, mild to moderate distal sensory loss, depressed tendon reflexes and high-arched feet (Bird and Adam, 1993). Weakness of the feet and of lower leg muscles may result in foot drop and induces a high-stepped gait with frequent tripping or falls. Foot deformities, such as high arches and hammertoes are also characteristic due to weakness of the small muscles in the feet. In addition, the lower legs may take on an "inverted champagne bottle" appearance due to the loss of muscle bulks. Symptoms of CMT1A disease usually begin in adolescence or early adulthood (between age 5 and 25 years). This disease is characterized by progressive worsening during the adulthood. Later, weakness and muscle atrophy will involve the hands, resulting in difficulty with fine motor skills. The severity of symptoms is quite variable in different patients and even among other diseased family members. Progression of symptoms is gradual. Pain can range from mild to severe, and some patients may need to rely on foot or leg braces or other orthopaedic devices to maintain mobility; 5% of individuals become wheelchair dependent. Although CMT1A is not a fatal disease, it is considered as chronically debilitating.

CMT1A is a subtype of CMT Type 1. CMT1A is caused by duplication of the *PMP22* gene at chromosome 17p11.2 diagnosed by genotyping. Peripheral myelin protein 22 (PMP22) is a 160 amino acid compact myelin protein with four transmembrane domains. Duplication of *PMP22* is associated with an increased messenger ribonucleic acid (mRNA) in peripheral nerves; it results in an abnormal myelination process induced by an unknown mechanism *(Gabriel, Erne et al., 1997; Vallat, Sindou et al.*, 1996). The moderately elevated expression of this gene disrupts the normal myelination process that concerns neuron and Schwann cells, slows down the signal transmission along the axons and deprives them of important neurotrophic factors normally provided by mature Schwann cells. So, over-expression of the wild-type PMP22 protein is responsible for CMT 1A, which is the most frequent demyelinating subform of CMT disease (Bird and Adam, 1993; Fortun, Go *et al.*, 2006; Patzko and Shy, 2011).

CMT1A accounts for 70 to 80% of CMT Type 1 patients and for 40 to 50% of all CMT patients (Bird and Adam, 1993; Dubourg, Tardieu *et al.*, 2001; Boerkoel, Takashima *et al.*, 2002; Reilly, 2005; Pareyson, Scaioli *et al.*, 2006; Shy, Chen *et al.*, 2008). The prevalence of CMT1A is estimated to be of 1.4 per 10,000 people in the European Community.

There is currently no approved treatment available to cure CMT1A disease, nor medical guidelines for the management of the disease (Mathis, Magy *et al.,* 2015).

Supportive therapies mainly address aspects of neuropathic pain and limb deformities. The most useful supportive treatments include treatment of pain (anti-inflammatory/analgesics, anti-depressants or

anti-convulsive drugs for neuropathic pain) (Shy, 2006), physiotherapy (muscle strength training), occupational therapy, orthopaedic devices (including braces and high top shoes) as well as orthopaedic surgery. However these treatments are not sufficient to limit impairment of motor function and worsening of disability.

Ascorbic acid (AA) was shown to promote myelination *in vitro* and to possibly decrease PMP22 expression (Passage, Norreel *et al.*, 2004; Kaya, Belin *et al.*, 2007). *In vivo*, ascorbic acid was shown to reduce the severity of neuropathy in a rodent model of human CMT1A: transgenic mice overexpressing PMP22 (Passage, Norreel *et al.*, 2004). To the best of our knowledge, the study was not replicated and no studies were conducted with ascorbic acid on other animal models of CMT1A. On the basis of these data, several clinical trials were initiated to assess the efficacy of ascorbic acid in patients with CMT1A. A meta-analysis of available clinical trial data suggested that high doses of AA may provide significant benefit in patients with CMT (Young, De Jonghe *et al.*, 2008).

Six additional published clinical trials assessed 1- or 2-year AA treatment but failed to show a significant clinical benefit:

1- In a pilot placebo controlled Dutch trial, ascorbic acid had no significant effect in five patients (aged 14–24 years) treated with 2 g/day for one year compared with six patients on placebo (aged 13–24 years) (Verhamme, de Haan *et al.*, 2009).

2- In an Australian trial, 42 children treated with an equivalent dose (30 mg/kg per day) for one year failed to show a significant improvement compared with 39 children on placebo (Burns, Ouvrier *et al.*, 2009). In a post-hoc analysis, five children treated with ascorbic acid had a large increase in motor conduction velocity in the median nerve.

3- In a pilot, open-label, cohort-controlled US trial, 12 patients (aged 31-41 years) treated for 2 years with a high dose (5 g/day) of ascorbic acid did not show any improvement as compared with a cohort of 10 untreated CMT1A patients. Further, tolerability of this high dose of ascorbic acid appeared to be poor: only 42% of patients could tolerate 5g for 2 years, and 50% developed prominent diarrhoea and/or gastric bloating (Toth, 2009).

4- In a randomized French trial 179 adult patients were treated for one year with one of two doses of ascorbic acid (1 or 3 g/day) or placebo. Ascorbic acid was safe and well tolerated, but failed to show significant benefit. A post-hoc analysis of the clinical sub score of the CMTNS, the CMTES, showed however that the high dose group scored significantly better than the other groups (Micallef, Attarian *et al.*, 2009).

5- A 2-year placebo-controlled multicenter trial conducted in Italy and in the UK in 271 patients (aged 18-70 years) with DNA proven CMT1A failed to show significant benefit of ascorbic acid (Pareyson, Reilly *et al.*, 2011).

6- An US randomized, placebo-controlled, clinical trial in 110 subjects with CMT1A, aged 13 to 70 years, treated with AA or placebo (randomization 1:4) over a period of 24 months was recently published. The trial was designed to determine whether it would be futile to carry out a larger randomized, double-blind, placebo- controlled trial to examine the efficacy of high dosage AA in slowing the progression of CMT1A. The study failed to show efficacy of AA 4g/d compared to placebo and definitely closed any hope in this potential treatment. (Burns, Ouvrier *et al.*, 2009; Micallef, Attarian *et al.*, 2009; Toth, 2009; Verhamme, de Haan *et al.*, 2009; Pareyson, Reilly *et al.,* 2011; Lewis, McDermott *et al.*, 2013).

Blockage of the progesterone receptor also shown to improve clinical features in CMT animal models, but was never tested in patients with CMT1A.

To the best of our knowledge, no other drug is currently being investigated in clinical stage in this pathology.

Considering the debilitating nature of the disease and the absence of a specific therapy, there remains a pressing unmet medical need for an efficacious and safe treatment for CMT1A.

6. 2 Pharnext approach and PXT3003 selection

Pharnext is repositioning off-patent drugs (marketed in Europe and North America) reformulated and combined in low doses associations for the treatment of novel indications with a high unmet medical need through the application of an innovative approach. The underlying principle behind this approach is "network pharmacology" in which multiple targets of a disease are treated by combinations of low dose of repurposed safe drugs. The constituents of specific combinations are selected on the basis of a genetic understanding of the specific disease molecular targets and the constituent's pharmacological mechanisms of action. In this approach, doses of individual drugs are well below the range of the currently recommended human doses for their approved indications.

As a first step in our drug discovery program, we performed a systematic analysis of available data to define a group of signalling pathways important for peripheral nerve structure and function affected in CMT1A disease. Among them, modular pathways known to affect myelin gene expression such as cAMP-dependent mechanisms, neurosteroid signalling and the Akt/Erk pathway were of particular interest. We hypothesized that these modules are integrated as a unified system that is influenced by G protein coupled receptors (GPCRs) leading to the differential regulation of genes for peripheral myelin proteins. Since PMP22 is not only a structural component of myelin, but may have signalling functions in Schwann cells, its transcriptional control could be different from "classical" structural myelin genes such as *MPZ*. The topology of these putative regulatory networks permitted us to suggest that drugs acting on different GPCRs could cause a more potent and robust influence when combined. Thus, we have focused on the drugs able to modify relevant branches of GPCR signalling. This class of compounds is functionally acting on multiple pathways and is represented in approved Pharmacopeia. This allowed us to apply additional safety criteria for their selection. We also selected drugs which could be relevant for other aspects of peripheral nerve physiology that are affected in CMT1A, particularly drugs potentially promoting neuronal protection. This process was performed and allowed to select a lead compound: PXT3003 consists of a combination of very low doses of three substances (RS)-baclofen, naltrexone hydrochloride and D-sorbitol, which are thought to act in different ways in Schwann cells and neurons to limit the production of PMP22 in patients with CMT1A.

Baclofen ([RS]-form) is a centrally acting skeletal muscle relaxant. It is indicated at doses up to 100-120 mg/day (depending on the EU countries) to control spasticity and pain in people with multiple sclerosis and spinal disorders. As potent agonist of GABA-B receptors, baclofen is expected to negatively regulate the transcription of *PMP22* gene in Schwann cells, most likely, via the cAMP-dependent silencer element (Magnaghi, Ballabio *et al.*, 2004; Magnaghi, Ballabio *et al.*, 2006).

Naltrexone (N-cylopropylmethylnoroxymorphone) is a potent opiate antagonist with only very weak agonist properties marketed for opiate and alcohol dependence. Naltrexone blocks opioids by binding competitively at opioid receptors. In opioid free individuals, naltrexone administration at the approved therapeutic dose (i.e. up to 50 mg/day) has been associated with a predictable profile of serious adverse or untoward events. At very low doses (0.1 mg/kg), it was shown to raise endogenous endorphin release (Hytrek, McLaughlin *et al.*, 1996) and works also as a chemical chaperone and therefore, can increase cell surface targeting of cognate opioid receptors (Leskela, Markkanen *et al.*, 2007). Naltrexone is expected to potentiate canonical opioid receptors signalling coupled to activation of Gαi proteins and

thus to potentiate adenylate cyclase-inhibiting effect of endogenous opioids on the level of expression of PMP22, through a mechanism complementing and potentiating baclofen's mechanism of action.

Sorbitol (d-Sorbitol, glucitol) is a polyhydric alcohol with about half the sweetness of sucrose. Sorbitol occurs naturally and is also produced synthetically from glucose. It is used as a laxative (at doses up to 15 g/day) and in irrigating solutions for some surgical procedures. It is also used in many manufacturing processes, as a pharmaceutical aid or excipient, and in several research applications. Sorbitol seems also to play an important role in peripheral nerve physiology (Maekawa, Tanimoto *et al.*, 2001) since it can bind with a high affinity (in the 1 µM range) to muscarinic receptors (Zhu and Li, 1999; Loreti, Vilaro *et al.*, 2006) that play an important role in PMP22 expression and improve the folding of proteins (Howard, Fischer *et al.*, 2003; Kumar, 2009), the feature that is deficient in CMT neuropathy. D-sorbitol has been selected as a component of the fixed-dose combination product as regards to its potential ability to impact the expression of *PMP22* gene and other aspects of CMT disease through mechanisms differing from those of baclofen and naltrexone.

The combined actions of the three substances at low dose are expected to improve the function of the myelin sheath, improving signal transmission between nerve cells and relieving the symptoms of the disease as demonstrated in previous Pharnext *in vitro* and *in vivo* research studies (Chumakov, Milet *et al.*, 2014).

6. 3 PXT3003 - Summary of non-clinical studies

In vitro characterization of the activity of the combination PXT3003 and of its individual drugs on myelination induction and PMP22 expression down-regulation not only showed the superiority of PXT3003 to its individual components, but also proved the positive synergy between its components.

In vivo, relevant data in the CMT1A transgenic rat model clearly demonstrated the efficacy of PXT3003 on functional, histological and electrophysiological parameters. In the mouse nerve crush model, also used to assess CMT1A disease, PXT3003 improved electrophysiology as well as axonal myelination and regeneration, and restored synergistically the functional behaviour of mice in contrast to single drugs that showed not effect individually (Chumakov, Milet *et al.*, 2014).

Please refer to the Investigational Brochure (IB) for more detailed information.

6. 4 PXT3003 - Summary of clinical studies

Pharnext has conducted a single first-in-human Phase II, randomized, double-blind, parallel-arm, multicenter, placebo-controlled study evaluating 3 different oral dose strengths of PXT3003 in adult outpatients, with CMT 1A (CLN-PXT3003-01) (Attarian, Vallat *et al.*, 2014).

The primary objective of the study was to assess the clinical and laboratory safety and tolerability of the 3 doses of PXT3003. The secondary objective was to obtain preliminary data on the efficacy outcome measures on clinical scores, functional tests and electrophysiological parameters although no formal calculation of sample size has been performed.

Eighty patients aged 18-65 years with mild to moderate CMT1A confirmed by genotyping were included in this trial and randomized into four balanced groups to receive twice daily (in the morning and in the evening) in a 1:1:1:1 ratio per oral administration Low-Dose (RS-baclofen 0.3 mg, naltrexone hydrochloride 0.035 mg, D-sorbitol 10.5 mg), Intermediate-Dose (RS-baclofen 0.6 mg, naltrexone hydrochloride 0.07 mg, D-sorbitol 21 mg) or High-Dose (RS-baclofen 3 mg, naltrexone hydrochloride 0.35 mg, D-sorbitol 105 mg) of PXT3003 (termed LD, ID and HD respectively in the following) or placebo during one year. Inclusion criteria included in particular CMTNS score of ≤ 20 at baseline, corresponding to mild to moderate severity.

The demographic baseline characteristics comparable in the 4 treatment arms included in particular a CMT1A with a mean time since diagnosis of 8.2 years and a mean CMTNS score of 13.9.

The study met its primary endpoint that was to demonstrate the safety and tolerability of the 3 doses of PXT3003 administered twice daily over a year. The incidence of treatment-emergent adverse effects (TEAEs) was similar across the 4 treatment arms (47% in the placebo arm, and respectively 23%, 33%, 31% in the LD, ID, HD arms (P = 0.48 Fisher exact test)) and the majority of related TEAEs were mild. TEAEs with a moderate severity were reported in only 3 patients: 2 in the HD arm (abdominal cramps and diarrhea; nausea), 1 in the ID arm (palpitations). Moreover, no relevant changes in vital signs, Electrocardiogram (ECG), or any of the chemistry or haematology test results were observed.

The 3 doses of PXT3003 were shown to be safe as validated by the independent Data Monitoring Committee (DMC) along the study and as reported in the Development Safety Update Report (DSUR) (29-Nov-2011 to 28-Nov-2012).

Efficacy data of PXT3003 obtained from this phase II study on clinical scores, functional tests and electrophysiological parameters showed that the highest tested dose (HD) was effective compared to the other dose groups: for most of the efficacy outcomes, the best improvement was observed in the HD group.

A step down search of the Minimum Effective dose identified the High Dose as the most promising dose. From there, the HD was considered as the effective dose and compared to the other groups considered together (termed 'PLI' in the following).

The HD showed consistent evidence of modest improvement compared to placebo and the other doses, particularly on the two main clinical scores CMTNS and ONLS, with a significant improvement of respectively of 8% (P = 0.042; 90% CI: 0.4% - 16.2%) and 12.1% (P = 0.024; 90% CI: 2% - 23.2%) in the HD group versus the pool of all other groups, appearing to be the most sensitive clinical endpoints to treatment despite their quasi-stability over one year under placebo.

The proportion of responders defined as patients not deteriorating at 12 months on the percentage of change from baseline averaged over the CMTNS and ONLS was also significantly higher in the HD group (79%; Relative Risk of 1.66, p = 0.01) compared to placebo and the other groups (all around 48%). Significant evidence of responders after only one year of treatment under High dose, with apparently less severe baseline characteristics, would suggest a possible 'disease modifying' effect for PXT3003.

Among the secondary functional measures, 6MWT and Grip showed a trend of improvement in the HD group compared to the pool of all other groups. The cumulative contribution of PXT3003 to the improvement of functional measures was assessed through the significance of the O'Brien's OLS test (O'Brien 1984) which confirmed a good improvement in the HD group when compared to the pool of all other groups (p = 0.051).

At the electrophysiological level, myelin function assessed by conduction velocity and distal latency showed also improvement: Distal Motor Latency was significantly decreased in the HD group when compared to Placebo (8% of improvement, p = 0.038), and Sensory Conduction Velocity was significantly increased when compared to Placebo (26.6% of improvement, p = 0.00037) and to the pool of all other groups (20.1% of improvement, p = 0.03).

Albeit the therapeutic effect seems modest, it is striking that, over only one year, CMTNS and ONLS both improved from baseline under HD while these scores were not changed in patients under placebo. This might be explained by a functional improvement of dysmyelinated non degenerated axons, i.e. a decrease of axons suffering which would pair with a lower risk of degeneration. This is consistent with the putative mechanism of action of PXT3003 that may impact Schwann Cells function as it was shown to improve impaired myelination in PMP22 transgenic Rat treated after symptoms onset.

This first-in human study demonstrated the good tolerability and safety of the 3 tested doses of PXT3003 and also provided preliminary evidence of efficacy for PXT3003 at the highest dose tested (HD) on the selected relevant clinical and electrophysiological outcome measures. This coherent set of data

suggests that PXT3003 deserves further clinical investigation in a confirmative pivotal study.

Finally, as CMT 1A patients are known to deteriorate rather slowly, then goals need to focus on detecting actual improvement in adult patients rather than just slowing disease progression. Significant evidence of responders after only one year of treatment under high dose, with apparently less sever baseline characteristics, would suggest a possible 'disease modifying' effect for PXT3003.

Consequently based on these considerations, a further clinical investigation with PXT3003 in a phase 3 pivotal confirmatory registration study in a wider population is justified and could provide confirmation of its efficacy and positive benefit-risk ratio and also additional insights on its mode of action.

6. 5 PXT3003 Summary of the known and potential risks and benefits to human subjects

PXT3003 consists of a combination of very low doses of three substances: (RS)-baclofen, naltrexone hydrochloride and D-sorbitol, which are thought to act in different ways to limit the production of PMP22 in patients with CMT 1A.

The three substances are well established drugs/excipients currently used for more than 30 years at higher doses and in other indications:

- **baclofen** is approved in the treatment of spasticity resulting from diseases such as multiple sclerosis, with recommended dose of 20 mg t.i.d. to q.i.d., i.e. 60 to 80 mg/day, up to 120 mg/day maximum. In France, baclofen is also currently tested in alcohol withdrawal, and can be prescribed under RTU conditions (Temporary Recommendation for Use on Off-label Baclofen) at doses up to 300 mg/day. In PXT3003, baclofen is used at doses 1/5 to 1/10 of the recommended dose.

- **naltrexone** is approved in the treatment of alcohol or cocaine dependence with recommended dose of 50 mg/day. In PXT3003, naltrexone is used at doses 1/35 of the recommended dose.

- **sorbitol** is used as excipient or is approved as osmotic treatment of constipation with a recommended dose of 5 to 15 g/day. In PXT3003, sorbitol is used at doses 1/35 of the recommended dose.

Safety profiles of baclofen and naltrexone in particular are well documented (Please refer to Investigator Brochure)

Baclofen current product labelling in its approved indication for spasticity specifies that, at the approved doses, it may cause transient drowsiness, dizziness, weakness, headache, seizures, nausea, vomiting, low blood pressure, constipation, confusion, respiratory, depression, inability to sleep, and increased urinary frequency or urinary retention. Special warnings and precautions for use must be taken in severe psychiatric disorders, epileptic manifestations, in patients already receiving antihypertensive therapy, suffering from cerebrovascular accidents or from respiratory, hepatic or renal impairment, with a history of peptic ulceration, with pre-existing sphincter hypertonia with risk of acute retention of urine, with liver diseases and elevated SGOT, alkaline phosphatase and with diabetes mellitus. Baclofen is contraindicated in hypersensitivity to baclofen or any of the excipients, in patients with rare hereditary problems of galactose intolerance or Lapp lactase deficiency or glucose-galactose malabsorption, active peptic ulceration and porphyria.

Consequently careful titration of dosage from 5 mg t.i.d. to 20 mg q.i.d. is recommended until the patient is stabilized. This is particularly relevant if the patient is ambulant in order to minimize muscle weakness in the unaffected limbs or where spasticity is necessary for support. The incidence of adverse effects during oral administration of baclofen can be however reduced by slowly increasing the dose to optimal therapeutic levels.

Baclofen may increase the sedative effect of alcohol and CNS depressants such as barbiturates, opioids, benzodiazepines and other anxiolytic drugs, hypnotics, neuroleptics, antihistamine H1 compounds, centrally acting antihypertensive drugs, sedative antidepressants. Baclofen may increase the side effects of levodopa (confusional state, agitation, hallucinations) and the antihypertensive effect of antihypertensive compounds. Baclofen may induce increase hypotonia if co-administered with tricyclic antidepressants.

However, taking in account the low doses of baclofen in PXT3003, the warnings described can be nuanced.

Naltrexone current product labelling in its approved indication for opioid and alcohol dependence specifies that the most frequent adverse effects reported with naltrexone are gastrointestinal effects; these can be minimized by taking the drug with a meal, and are not likely to occur at the low doses administered in PXT3003.

Naltrexone is contraindicated in particular in patients with acute hepatitis or liver failure, currently dependent on opioids or in conjunction with an opioid containing medication, who have demonstrated hypersensitivity to naltrexone hydrochloride and who have severe renal failure.

In alcohol dependence, naltrexone even at high daily dose (much higher than the very low dose used in PXT3003) is considered as a safe medication. Control of liver values prior to initiation of treatment is however recommended, as naltrexone has been reported to induce dose-related hepatotoxicity. However, evidence of hepatotoxic risk has not been demonstrated at the doses usually recommended, and it should thus be of no relevance for the low doses administered in PXT3003.

Sorbitol is used as an osmotic laxative but is also naturally present in fruits and is widely used as a sweetener, a food additive and an excipient. The main adverse effects of sorbitol when used as laxative at high doses are abdominal cramps, diarrhoea and catharsis. These adverse events should not be relevant at the doses employed in PXT3003.

For each of these drugs, the FDA and the European regulatory bodies considered the risk/benefit ratio to be appropriate for the conditions specified on the labels. Pharnext is proposing the repositioning of these drugs in a different indication, CMT1A, a change that may impact the risk/benefit ratio that supported the original marketing applications. However, as the dose of each drug used in the PXT3003 compound was considerably lower than that currently used in their approved indications (5 to 35 times less), it was assumed that no meaningful alterations in the risk/benefit analysis could arise, particularly in support of an orphan disease indication with no alternative therapy available. Overall, the preclinical safety pharmacology and toxicology profile of the drugs suggested that their use was appropriate in other indications.

The new fixed combination of low doses of the 3 drugs baclofen, naltrexone, and sorbitol, **PXT3003** was administered to human in the first Phase II clinical trial conducted on 80 CMT1A patients treated during 12 months. In total 61 patients were exposed to PXT3003 during one year. The clinical safety and tolerability of PXT3003 was shown to be excellent for the 3 studied doses, allowing investigating PXT3003 in a larger and longer Phase III study.

In conclusion, taken into account the low doses of each product (baclofen, naltrexone, sorbitol) used in PXT3003 and the good safety profile of the product as shown in the phase II clinical trial, we can consider the risk/benefit ratio of PXT3003 to be favourable. This consideration is again in favour of a further clinical investigation in a pivotal confirmatory phase III clinical study.

7. RATIONALE

CMT1A is a severe disease associated with a high morbidity. CMT1A has a substantial impact on the quality of life and day-to-day functioning for patients. It is a slowly progressive and debilitating hereditary neurodegenerative disease with an unmet medical need.

The first double-blind randomized phase II clinical trial, conducted on 80 CMT 1A adult patients treated during one year, provided the preliminary clinical evidence of efficacy of PXT3003 showing consistent improvement on most of the efficacy outcomes with one of the 3 doses tested compared to placebo, as well as the confirmation of its good tolerability and safety profile.

Thereby, PXT3003 has demonstrated a substantial improvement on clinically significant endpoints and on electrophysiological markers, while also showing a good safety profile. PXT3003 induced an improvement beyond a stabilization of the disability suggesting a reversion of the disease progression.

Based on these encouraging results, an orphan drug status was granted to PXT3003 in CMT1A by both the EMA and the FDA in March 2014, and Pharnext has decided to continue the development by planning a confirmative trial in a wider population. It will be a double blind, randomized, placebo-controlled, parallel group pivotal phase IIB/III study testing 2 doses of PXT3003 in adult patients with CMT1A treated for 15 months.

Considering the significant dose effect shown in the previous phase II study with improvement of most of the outcomes only with the highest dose it is assumed that the effect of the drug is just beginning with this HD and then that a higher dose which could be the double of HD should be tested to maximize the potential for treatment benefit.

Moreover, as there is no approved specific treatment in CMT1A, there is no active comparator to introduce, as usually done in such phase III clinical trial; placebo will then be used as control. PXT3003 or placebo will be given on top of standard cares. So, the study will combine a phase IIB for dose ranging and a Phase III as confirmative pivotal study.

The 2 tested doses will be then compared to placebo within 3 balanced groups randomized (1:1:1):

- Dose 1, corresponding to the highest dose (HD) from the previous phase II study,
- Dose 2, a new dose with double amount of each active components of PXT3003 (*i.e.*, HD X 2),
- Placebo.

The first dose (Dose 1) corresponds to the highest dose found safe with preliminary evidence of efficacy in the phase II clinical study. Based on the “dose-effect” observed in this phase II study, and the increased effect among the 3 tested doses with positive results shown only on the highest dose (HD: 3 mg baclofen, 0.35 mg naltrexone and 105 mg sorbitol, given twice per day), it is assumed that a higher dose could also be tested as an additional dose for a further clinical trial.

This additional dose is selected with the same ratio, based on an exploratory analysis of PK-PD relationship of the drugs and the improvement in the main endpoints, and taking into account the limitations regarding the baclofen dosage which should not be increased too much to guaranty the good tolerability, for safety reasons. Based on these considerations, a double dose (6 mg baclofen, 0.70 mg naltrexone and 210 mg sorbitol), i.e. two-fold of the HD as described previously, will be used twice daily in the proposed phase III study. This second dose, which has never been tested before and which is expected to be more active, will be tested independently as an additional dose. In order to improve baclofen tolerability, the dosage will be titrated by administering half dose during the two first weeks of the study. Therefore the study should provide efficacy, safety and PK data on this additional higher dose.

PXT3003 is a combination of 3 well-known drugs directed at multiple therapeutic targets to improve treatment response in the demyelinating CMT1A disease, but none of the 3 drugs have already been

used in this indication, neither any have approval in the targeted indication.

During a pre-IND meeting, the FDA advised to refer to the Guidance for Industry: *Codevelopment of two or more new investigational drugs for use in combination, June 2013*.

In this guidance, co-development option is recommended in some particular situations, even if generally it provides less information about the clinical safety and effectiveness and dose-response of the individual new investigational drugs intended to be used in combination than would be obtained if the individual drugs were developed alone.

The guidance raises particular circumstances justifying an exemption from the requirement to perform studies with factorial design testing individual drugs compared to the combination when they have limited utility.

This guidance also specifies that:

> "*in some situations an alternative design may be useful when the drugs in the combination cannot be administered as monotherapy, particularly: if in vitro studies, in vivo animal models, or phase 1 or other early clinical studies indicate that the individual investigational drugs in the combination cannot be administered separately in clinical trials in the disease of interest (e.g., because such testing would involve administering treatment known to be ineffective as monotherapy and it is not ethically feasible), then the contribution of the individual drugs do not need to be demonstrated using a factorial design."*

These conditions are fulfilled by PXT3003:

- CMT1A is an orphan disease and a serious condition affecting the day-to-day quality of life of patients.
- There is a strong biological rationale for use of the combination, *e.g.* the agents modulate distinct targets in the same molecular pathway. The three drugs baclofen, naltrexone and sorbitol were selected on the basis of bionetwork pharmacology, and are down-regulating PMP22 mRNA over-expression.
- The three drugs when used alone at the low doses proposed in the combination have limited or absent efficacy in CMT1A *in vitro* and *in vivo* models, while the combination showed *in vitro* its superiority to improve synergistically myelination and down-regulate PMP22 expression, and *in vivo* not only restored the functional behaviour of CMT1A transgenic rats, but also the behaviour of crushed mice synergistically in contrast to single drugs that showed no effect individually.
- Administering treatment known to be ineffective as monotherapy is not ethically feasible, particularly in a rare disease such as CMT1A which is slowly progressive and would need a long time of observation.

This support the decision to test only the combination PXT3003 compared to placebo in the next clinical phase III.

Moreover, PXT3003 will be administered on top of standard of care (SOC), consisting of supportive therapies (authorized pain killers, physiotherapy, occupational therapy, and orthopedic devices) in an add-on design comparing the combination plus SOC to placebo plus SOC.

The current clinical trial will be then a registration pivotal phase III study to confirm, first the clinical efficacy of PXT3003 (primary objective) tested with 2 doses for 15 months in a double-blind randomized placebo-controlled design, and second the good tolerability and safety profile and the positive benefit-risk ratio of the product.

The study design has been prepared based on the previous experience in phase II with PXT3003 in CMT1A, and following the recommendations of a board of clinician CMT experts; it is also in accordance

with the recommendations of both European and US Regulatory Agencies who provided scientific advise through the process of *Protocol Assistance* for the EMA and *Special Protocol Assessment* for the FDA. With this pivotal study, the final goal for Pharnext is to justify and support a claim for a Marketing Authorization Approval (MAA) for PXT3003 in the treatment of CMT1A.

Considering the limitation to detect clinical changes within a short timeframe (*i.e.* 12 months), particularly in a disease characterised by a slow progression, there is no consensus on the clinical primary and secondary efficacy endpoints to evaluate investigational drugs in CMT1A. In the absence of FDA or EMA guidance relative to this specific disease, Pharnext initially referred to the only known recommendations on this disease published by the 136th ENMC International Workshop: Charcot Marie Tooth Disease Type 1A – 8-10 April 2005 (Reilly, de Jonghe *et al.*, 2006), and suggested using both the CMTNS and the ONLS as co-primary endpoints in order to assess the effect of PXT3003 on disease impairment and disability.

Concerns were raised by the CHMP/EMA on the poor sensitivity to change of CMTNS. In their recommendation to propose a primary endpoint assessing clinically meaningful differences, they provided reluctance for proposals based on composite z-score combining CMTNS and ONLS, arguing the possibility of global statistical significance whereas at least one of the endpoints should not have a clinically meaningful effect.

In parallel, the FDA expressed concern about CMTNS. While it is commonly used to assess disease severity, CMTNS may not be appropriate to evaluate the potential clinical benefit of a drug given that it is a composite score based on patient signs, symptoms and neurophysiological measures, with potentially different meanings and interpretation. The FDA advised to select a primary endpoint more directly related with drug benefit: in particular ONLS might be more appropriate as a specific disability estimate with functional scale grades for legs and arms.

The other usual endpoints will be used as secondary endpoints and they will be hierarchized as clinical, functional, electrophysiological and other exploratory endpoints. Secondary endpoints should be ordered in a hierarchical manner with statistical adjustment for multiplicity.

Out of these points, both agencies endorsed the proposed study population, the choice of doses and the key points of the design.

Therefore, if this single pivotal phase III study provides positive confirmatory results, it should be sufficient to support the marketing application of PXT3003 in the treatment of CMT1A adult patients.

8. TRIAL DESCRIPTION

8.1 Trial Objectives

The primary objective of this double-blind study is to assess the efficacy of two doses of PXT3003 compared to Placebo on the disability measured by the ONLS clinical score in CMT1A patients treated for 15 months

The Secondary objectives are to assess:

- The efficacy of two doses of PXT3003 compared to Placebo on other outcomes such as impairment clinical score (CMTNS-V2), functional tests (Walking test, QMT, Nine Hole-Peg test), electrophysiological parameters and measures of quality of life.
- The safety and tolerability of two doses of PXT3003 compared to Placebo;
- PK parameters of PXT3003 components (baclofen, naltrexone and 6β-naltrexol) in the 2 tested dosages of PXT3003;
- The change over time of potential blood biomarkers;
- Molecular changes in skin biopsy, when this procedure will be possible (ancillary sub-study);
- And new potential imaging biomarkers by leg MRI, when this procedure will be possible (ancillary sub-study & centralized reading).

8.2 Trial design

This is an international, multi-center, double-blind, randomized, placebo-controlled, phase III prospective study, comparing 2 doses of PXT3003 to placebo in parallel-groups, in outpatients presenting CMT1A disease. The study will be conducted in at least 20 European and US centers.

8.3 Population to be studied

The study will be performed **in a total of at least 300 patients** presenting a diagnosis of CMT1A, genetically proven, of mild to moderate severity (assessed by CMTNS-V2 score between 2 and 18), with muscle weakness in at least foot dorsiflexion, NCV ≥ 15 m/sec. The patients will be randomized in investigating sites in various European countries (such as France, Germany, UK, NL, Italy,…) and in US.

8.4 Study endpoints

8.4.1 Efficacy endpoints

8.4.1.1 Primary efficacy endpoint

The primary efficacy endpoint will be the main effect of the studied treatment on the improvement of disability measured by the Overall Neuropathy Limitation Scale (ONLS) score, summarized at 12 and 15 months defined by: **mean change of the ONLS from baseline to the two post-baseline measures at 12 and 15 months**.

Considering that ONLS is the preferred assessment method of disability, a clinically relevant endpoint in CMT1A, and that it has recently been shown to be more sensitive to change than CMTNS, ONLS is selected as primary endpoint.

8.4.1.2 Secondary efficacy endpoints

In the context of an orphan disease, when there are no ideal endpoints, it might be acceptable to assess multiple endpoints and to observe their outcomes. However, they have been selected according to our experience from the previous phase 2 study, and they are hierarchized as following:

- Responders Rate to PXT3003 therapy defined as a patients improving on ONLS at end of treatment.
- Clinical and functional tests:
  - Arm and leg sub-items of ONLS,
  - Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNS-V2*)*, total score and sub-items,
  - Nine-Hole Peg Test (9-HPT) performed on the non-dominant hand,
  - Hand grip Quantified Muscular Testing (QMT) and foot dorsiflexion QMT performed on both sides,
  - Time to walk 10 meters,
- Exploratory efficacy endpoints:
  - Electrophysiological parameters assessing sensory and motor responses of ulnar and radial nerves (non-dominant side):
    - Compound Muscle Action Potential (CMAP) on ulnar nerve,
    - Sensory Nerve Action Potential (SNAP) on radial nerve,
    - Nerve conduction velocity (NCV),
  - Quality of life measured by:
    - EuroQol 5-Dimensional Health-related Quality of Life scale (EQ-5D),
    - VAS on self-assessment of the individualized main impairment in daily activities defined at baseline with the patient,

8.4.1.3 Discussion on the choice of the efficacy endpoints

A. ONLS is a disability scale that was derived and improved from the Overall Disability Sum Score by (Graham and Hughes, 2006) to measure limitations in the everyday activities of the upper limbs (rated in 5 points) and the lower limbs (rated on 7 points) (See Appendix II). The total score goes from 0 (= no disability) to 12 (= maximum disability). Although the functioning of patients with peripheral neuropathy may be influenced by other factors in addition to their physical capacity, ONLS measures the perceived ability of the patient to move and fulfil normal life, and thus expected to be associated with Quality of Life. It was initially validated in a pool of 100 patients with diverse peripheral neuropathies (mainly of dysimmune origin but including 9 CMT patients, 11 patients with chronic idiopathic axonal polyneuropathy, and 13 patients with paraprotein-associated demyelinating neuropathy): it showed significant relationships with measures of impairment, disability and quality of life.

The 136th ENMC Workshop agreed in recommending the ONLS as the core disability scale for CMT1A trials (Reilly, de Jonghe *et al.*, 2006), and it reliability was subsequently further validated in 40 CMT patients (Solari, Laura *et al.*, 2008).

ONLS was shown to be more sensitive to change compared with CMTNS, as found in a recent analysis on the 34 CMT1A patients enrolled successively in two clinical trials. The first tested Acid Ascorbic (a phase II randomized placebo-controlled trial performed at three hospital sites from September 2005 to October 2008 on 180 patients (Micallef, Attarian *et al.*, 2009)), and the second was conducted 5 years later, testing PXT3003 (a Phase II placebo-controlled trial performed at six hospital sites from December 2010 to November 2012 on 80 patients (Attarian, Dubourg *et al.*, 2013)). During the five years between the two assessments, no modification on CMTNS, Charcot-Marie-Tooth Examination Score (CMTES) or motor and sensitive amplitudes were reported, while a significant increase of ONLS score was noticed. It is known that CMT1A is a progressive neurodegenerative disease and the natural progression of the disability during the 5 years between the two studies was shown by the ONLS while the CMTNS did not reflect the disease progression.

Considering that the ONLS is the best assessment method of disability, a clinically relevant endpoint in CMT1A, and it has been recently shown to be more sensitive to change than the CMTNS, the ONLS is selected as primary endpoint.

B. CMTNS is a specific scale designed to assess severity of impairment in CMT disease (Shy, 2005). Although not completely validated, it provides a single and reliable measure of CMT severity. It is a 36-point scale based on 9 items: 5 of them quantify impairment (sensory symptoms, pin sensibility, vibration, arm and leg strength), 2 activity limitations (motor symptoms arms and legs) and 2 electrophysiological data (amplitudes of ulnar Compound Muscle Action Potential [CMAP] and Sensory Nerve Action Potential [SNAP]). Increased scores indicate a worsening of the function: the scores categorize a disability as mild (0-10), moderate (11-20) and severe (21-36).

While CMTNS score is commonly used to assess disease severity, it may be problematic to evaluate the potential clinical benefit of a drug; as it is a composite score based on patient signs, symptoms, and on electrophysiological data with potentially very different meanings and interpretations, an objective analysis may be difficult.

Nevertheless, CMTNS is an accepted measure of CMT severity, but its sensitivity to change is debated (Reilly, Shy *et al.*, 2010). Some CMTNS components are apparently not sensitive enough, and floor/ceiling effects do occur. For instance, if the patient had surgery (fixation of the ankle), the 'motor leg symptoms' definitively score 3; so, it is not possible to get a decrease of the score whatever it happens. The usefulness of the SNAP component was also judged to be limited as it is frequently absent in CMT1A patients which receive the maximum score on their entry visit, thus has a low sensitivity to change. (Komyathy, Neal *et al.*, 2013) pointed out that sensory and motor symptoms items result from subjective opinion from patients, concerning their leg and arm strengths and loss of sensation in their legs, and that pin sensibility, vibration and strength are based on a neurological examination which depends on patient cooperation and examiner consistency to obtain reproducible results. Finally, some measurement of the CMTNS, such as SNAP or vibratory sensation, may decrease normally with age; thus, scores could increase slightly as age for reasons independent of CMT (Shy, 2005).

A modified version 2 (CMTNS-v2) was issued in 2011 (Murphy, Herrmann *et al.*, 2011) to attempt to reduce floor and ceiling effects and to standardize patient assessment. This CMTNSv2 has not yet been tested in longitudinal studies, but it has still limitations to detect change as recently shown through a Rasch analysis, leading to the conclusion that "there is no current perfect outcome instrument for CMT" (Sadjadi, Reilly *et al.*, 2014).

More recently, an analysis by clustering assessed all clinical outcomes used in CMT1A trials and their contribution towards discrimination of disease severity including the 9 components of CMTNS score and 6 additional functional outcomes. Among them, only 5 items /9 of CMTNS score and 3 functional outcomes (10m timed walking test, 6 Hole Peg test and foot dorsal flexion dynamometry) were selected as discriminant to assess severity (Mannil, Solari *et al.*, 2014).

Although the CMTNS sensitivity in detecting the effects of a therapeutic intervention has never been demonstrated, it remains the only CMT-specific outcome measure (although not specific to CMT1A) and it was used as a primary outcome in main Ascorbic Acid clinical trials (Micallef, Attarian *et al.*, 2009; Pareyson, Reilly *et al.*, 2011; Lewis, McDermott *et al.*, 2013). Given the uncertainties regarding its sensitivity and the clinical meaningfulness of the effects that might be detected, it is proposed to use CMTNS-v2 as a secondary endpoint.

C. Nine-Hole Peg Test (9-HPT) *performed on non-dominant hand*

The 9-HPT is a simple timed test of fine motor coordination of extremities in the upper limbs. It measures the lag time needed by the patient to insert nine pegs in nine holes and to remove them (normal required time being 18 seconds).

9-HPT can be considered, at least, as an impairment measurement, although not directly measuring disability functions. In this regard, aggregating this test with other impairment/disability functions may take sense.

Restraining 9-HPT performed on the non-dominant hand is justified by the fact that the dominant hand might be often affected by the Carpal Tunnel Syndrome frequently associated to CMT disease, or compensatory mechanisms so the non-dominant 9-HPT is considered as a more specific measure of intrinsic CMT related status.

9-HPT has been widely used for acute and chronic acquired dysimmune neuropathies or for Parkinson's disease and recently in CMT clinical trials. Intra and inter-rater reliabilities were tested in 40 CMT patients by (Solari, Laura *et al.*, 2008) and were found to be excellent. But the sensitivity to change was not assessed, needing longitudinal studies.

Currently used in multiple sclerosis as a motor deficit measurement, 9-HPT involves strength (distal and proximal) and proprioception (sensory); thus, it gives information concerning proximal and distal parameters.

D. Hand grip Quantified Muscular Testing (QMT) and Foot dorsiflexion QMT performed on both sides

QMT is used to evaluate motor strength in CMT1A (Hogrel, Payan *et al.,* 2007; Shy, Chen *et al.*, 2008; Payan, Hogrel *et al.*, 2009). QMT testing bilaterally ankle dorsiflexion and handgrip was successfully used in previous CMT1A clinical trial testing AA.

The QMT has been successfully used to evaluate motor strength in fascio-scapulo-humeral myopathy and CMT1A (Micallef, Attarian *et al.*, 2009) in comparison to healthy control subjects. The following muscles will be evaluated as previously described: tibialis anterior (right and left) and hand grip (right and left). The best value on three consecutive and reproducible tests will be collected in the CRF for each muscle. Before the study, all examiners will attend training sessions and a separate technical document will detail the techniques and materials to be used for these evaluations.

Impairment of the muscular strength measured by hand grip and foot dorsiflexion seems burdened by a strong variability inter-judges and inter-patients, while foot dorsiflexion is non-assessable if the patient had surgery of the ankle. So, we expect more variability of the measures on the feet than on the hands.

The sum of motor strength + handgrip on both hands might constitute the *a priori* best justified aggregate measure. Foot dorsi-flexion will be also assessed on both sides.

These measures are considered as impairment, and not as disability. We can guess that the developed muscular strength is one direct result of the muscular power and is rather dependent on amplitudes.

E. 10 metres Walking Test (10mWT)

The walking tests are expected to be partly correlated with ONLS, CMTNS and QMT. However, in the previous clinical trials, 6-Minutes Walking Test (6-MWT) was used, but a clear training effect was shown along the successive visits in all groups, with no difference with the placebo group so that finally it does not seem to be relevant to evaluate CMT disease. The 6-MWT is time consuming and requires a large space to be practiced.

Better than an endurance test on a long distance, most of the interviewed experts prefer to test the speed to walk on a small distance as the limited dorsiflexion in CMT induces walk impairment particularly at start. The time to walk10 meters is proposed.

The 10m WT is simple to administer, standardized, reliable and valid evaluation of functional exercise capacity and gait that has been proven reliable in neurologic disorders (Watson, 2002; Tyson and Connell, 2009) and in CMT patients (Solari, Laura *et al.*, 2008). Results recorded are the time to walk 10 meters and the number of steps performed.

Even if walk tests have been proven reliable in other pathologies including neurologic disorders, their reliability and sensitivity are not established in CMT and need to be assessed. The walking test is sensitive to fatigue related changes and to ankle status (walk ability may be modified if orthese or surgery) and it correlates with established outcome measures. However it only reflects the ability to walk 10 metres in a controlled environment at a constant speed. The walking test is expected to be partly correlated with ONLS, CMTNS and QMT.

F. Electrophysiological parameters

Sensory and motor responses measured at ulnar and radial nerves on the non-dominant side:

- Compound Muscle Action Potential (CMAP) on ulnar nerve
- Sensory Nerve Action Potential (SNAP) on radial nerve
- Nerve Conduction Velocity (NCV)

For CMT, it is usual to measure motor and sensory amplitudes of one nerve (ulnar is recommended for CMAP and radial for SNAP in the modified CMTNS version 2).

CMAP appears as weakly reliable since affected by the positioning of the electrodes and hence is physician-dependent. NCV is a more reliable measure since relatively unaffected by the electrodes positioning and is only affected by the skin temperature.

CMAP measures conduction of nerve impulses better than the conduction velocities that are affected in CMT1A since a very early age. An improvement of the patient requires an increase of the CMAP. However, electrophysiological parameters are measured on more or less severely impaired and atrophic distal muscles, but it is well recognized that an improvement usually first appears in the less affected proximal parts. Consequently and in our context, the sensitivity of the CMAP remains limited. The same applies for NCV, but it is the CMAP that prevails.

Sensory measures (SNAP and SCV) are less reliable than motor ones due to their very high sensitivity to electrodes positioning. SNAP is affected by the cutaneous impedance that varies with the sub-dermal tissue thickness (~obesity). Moreover, in CMT1A, amplitudes are close to zero, so that conduction velocity is not measurable. These values are of a limited use. Finally, as missing value of SNAP might be a characteristic of severity, disregarding missing values for severe patients, and using for other patients may introduce a bias. Under a given threshold, amplitudes disappear as they stand below the lower level of detection or are measured on highly altered fibers; this anomaly can also be related to other non-specific factors, such as lesions of the skin). This 'grey zone' does not correspond to a zero but certainly to a very low value difficult to measure.

A quick axonal regeneration after a 1-year treatment is not realistic. However, an indirect recurrence of potentials is still plausible after resynchronisation of remyelinated fibers and summation of the potentials of each fiber. Indeed, the demyelination of fibers induces a desynchronisation leading to the dispersion of the electric signal which reduces its amplitude to zero. A positive effect after a 1-year treatment is more likely to be observed on the conduction velocities rather than on amplitudes.

The electrophysiological parameters considered here measure more a putative distal effect of the treatment rather than a proximal one that is however more likely to be observable at first. To the end to measure a proximal effect, electrophysiological measures on the sciatic nerve would represent an ideal alternative, but technical constraints are not well controlled.

In conclusion, electrophysiological parameters may provide pharmacodynamics information on the nerve integrity (Schwann cells and axons) in the distal part of the arm. CMAP on ulnar nerve and SNAP on radial nerve will be measured to fulfil the CMTNS modified version 2 items.

G. Quality of life (QoL) assessments

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

Quality of life endpoints should describe to which extent the disease is limiting life activities and impacts the overall Quality of Life or Well-being. So far, no such scale has been used, and no validated specific QoL scale has been used in CMT disease. In some AA trials, Short Form 36 Health Survey (SF-36) was used, but it did not show significant results. SF-36 is a quality of life questionnaire that was initially designed as a cardiovascular disease assessment. The questionnaire is very long to administer and questions are not usually well adapted to the impairment observed in peripheral neuropathies. The investigators of the phase II trial advised to withdraw this questionnaire for the phase III study and to choose an easier one: the EuroQol 5-Dimensional Health-related Quality of Life scale (EQ-5D) is short and easy to administer even if it is not validated specifically in CTM disease.

- VAS on self-assessment of the individualized main impairment in daily activities defined at baseline with the patient

VAS will be used for an individualized self-assessment by the patient of her/his main impairment in daily activities which will be defined at baseline; it will be re-evaluated with the patient at each visit of the follow-up (See Appendix 5).

In CMT no patient-reported outcome has been validated today. In recognition of the importance of patient input we intend to test such a new instrument, even if it is subjective that may provide information on the patient perception.

8.4.2 Safety endpoints

Safety and tolerability of PXT3003 will be compared to placebo on the following parameters:

- Incidence of Treatment Emergent Adverse Events (TEAEs); they will be evaluated by type/nature, severity/intensity, seriousness, duration, relationship to study drug, and outcome;
- Incidence of related TEAEs (including possibly and probably related TEAEs) with a moderate or severe intensity;
- Incidence of AE leading to withdrawal of study drug;
- Incidence of Serious Adverse Events (SAEs);
- Changes in physical examination, vital signs (blood pressure and and heart rate), 12-lead ECG, and laboratory data (hematology and blood chemistry).

The occurrence of AEs and SAEs is recorded from the time of signed informed consent until the end of the study. The pre-treatment period is defined as the time from informed consent up to the time of the first administration of IMP. The on-treatment period is defined as the time from the first administration of IMP up to time corresponding to the last administration of IMP.

All AEs and SAEs will be coded to a "Lower Level Term (LLT)", "Preferred Term (PT)", "High Level term (HLT)", "High Group Level Term (HLGT)" and associated primary "System Organ Class (SOC)", using the version of MedDRA (Medical Dictionary for Regulatory Activities) currently used by the sponsor at the time of database lock

8.4.3 Other exploratory endpoints

8.4.3.1 PXT3003 components plasma concentration

Plasma concentrations of baclofen, naltrexone and 6ß-naltrexol, PXT3003 components will be dosed on blood samples performed (on lithium heparinised tubes) at inclusion visit and at 6-month (V3), 12-month (V5) and 15-month (V6) visits to determine PK parameters of the 2 tested doses.

Blood samples will be performed at through (i.e. pre-dose in the morning) and at peak (i.e. 90 minutes after drug administration), and they will be stored at -80°C and analyzed in the central laboratory (Bertin Pharma, Orleans, France).

8.4.3.2 Blood biomarkers, gene expression analyses and DNA sequencing

Plasma samples for biomarkers identification will be performed at inclusion visit and at 6-month (V3), 12-month (V5) and 15-month (V6) visits, and they will be stored at -80°C.

This exploratory work on biomarkers should be considered only for research purposes and not as data that have to be delivered to patients or to health authorities at the end of this Phase III.

Pharnext has identified potential blood biomarkers (Tryptophan, Alanine, Serotonin, Thyroxin (T4), and free cholesterol) in the previous phase II that need to be confirmed in this phase III.

Meanwhile, other markers could be assessed for quantification studies, and thus identified later after the accomplishment of this clinical trial. On the other hand, from the same drawn samples, leucocytes will be isolated for gene expression studies (microarrays and PCRs).

Leucocytes will be isolated from an additional sample drawn at the inclusion visit only in order to realize DNA sequencing for all included patients after they have given their written informed consent for research purposes. One of the purposes of genome sequencing could be to advance the understanding CMT1A disease for the research community in general. It should be possible to identify genes that could change in response to PXT3003 treatment, which could confer them the property of pharmacodynamics candidates. Furthermore, gene expression analysis could be very valuable for the study of mechanisms occurring in CMT1A, which has never been performed before with such blood samples. For Instance, novel mutations in CMT1A patients, excluding those of CMT, could be discovered and associated with various mechanisms underlying the mildness or severity of the disease. On the other hand, correlations of sequencing data with clinical scores and endpoints are also relevant for the study of the pharmacodynamics of PXT3003 for a future potential development of personalized medicine. To this end, it is of interest to get benefit from such clinical studies as the one described here in this protocol to perform DNA sequencing because CMT1A patients are rare, which could substantially contribute to the improvement of the field. For these reasons, this sequencing study should be considered only for

research purposes and not as data that have to be delivered to patients or to health authorities at the end of this Phase III.

8.4.3.3 Biomolecular changes in skin biopsy (Optional ancillary sub-study)

Volunteer centers that agree to perform skin biopsies (according to their interest, available equipment and resources) will participate to this ancillary sub-study to assess candidate genes (biomarkers) by microarrays and RT-qPCR technics. Candidate genes will be selected based on ongoing assessments and analyses of skin biopsies derived from Phase II CMT1A patients and from other CMT1A cohorts generated by Pharnext. This exploratory study aims to identify genes that could change in response to PXT3003 treatment, which could confer them the property of pharmacodynamics candidates. Furthermore, gene expression analysis could be very valuable for the study of mechanisms occurring in CMT1A, which has never been performed before with such skin biopsy samples. Skin biopsies are of great value because of their rarity. This is why we would like to take the benefit of the Phase III trial to access these samples for research purposes.

One small punch biopsy will be performed at the ankle level of one leg at the inclusion visit (V1) and at the end of the treatment at the 15-month visit (V6). Separate protocol will define the methodology.

8.4.3.4 MRI of leg to assess muscle/fat index (Optional ancillary sub-study)

MRI is a method to identify areas of muscle atrophy and fatty infiltration in the legs that are hallmarks of disease severity and are due to the progressive degeneration of axons without concomitant re-innervation, resulting in progressive denervation of muscle. Del Porto *et al.* (2010) showed in CMT that changes in MRI signal intensity, reflecting muscle atrophy and fatty infiltration, are associated with changes in dorsiflexion strength and areas of acute denervation processes or injury. MRI shows areas where muscle has been replaced by fat, a process which occurs in neuropathies.

MRI of the leg will be performed at baseline and at the end of the study (Visit 6). In particular for example the anterior muscle compartment responsible for foot dorsiflexion (tibialis anterior, extensor hallucis longus, extensor digitorum longus and peroneus tertius) (del Porto, Nicholson *et al.*, 2010)..

Short Tau Inversion Recovery images will be acquired in the axial plane to delineate these structures and to assess changes in signal intensity as an indicator for acute denervation and/or possible injury (Gallardo, Garcia *et al.,* 2006).

The MRI examination will look for signal intensity alterations including muscle edema, fatty infiltration, and abnormal contrast enhancement. Increase of T1 signal intensity in the muscle belly due to fatty infiltration will be estimated in a semi-quantitative way, according to the Goutallier's classification (Schiefer, Mendonca *et al.*, 2015).

A specific technical manual will be written separately to ensure the standardization of MRI acquisition across all sites, and centralized reading will be organized.

9. SELECTION OF PATIENTS

The study will be performed in **genetically proven CMT1A patients**, **aged from 16 to 65 years, with mild to moderate severity and muscle weakness in at least foot dorsiflexion.**
It is planned to randomize at least **300 patients** [100 /arm] with the following selection criteria:

9.1 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 the Charcot-Marie-Tooth Neuropathy Score (modified version 2) 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- A written informed consent to participate in the study is signed by the patient and he is willing and able to comply with all the study procedures and the scheduled visits.

9.2 Exclusion criteria

Patients who have met all the above inclusion criteria listed will be screened for the following 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 an 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 completion of the trial;
6- Clinically significant abnormalities at the pre-study clinical examination, routine laboratory evaluations and electrocardiogram (ECG);
7- Elevated AST/ALT (>3 x ULN) and/or elevated serum creatinine levels (>1.25 x ULN);
8- History of recent alcohol or drug abuse or non-adherence with any 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- Women of child bearing potential not using highly-effective method(s) of birth control (ie, with low failure rate <1% per year) throughout the study and/or unwilling to be tested for pregnancy; Pregnancy or breast feeding;
11- History of safety issues or known hypersensitivity to baclofen, naltrexone or sorbitol, or to any of the individual components of PXT3003;
12- Any contraindication to use of baclofen (e.g. porphyria), naltrexone or sorbitol as defined in the national product labels;
13- Suspected inability to complete the study follow-up (transient visitors, tourists or any patient for whom the follow-up evaluation would be too difficult to appreciate for any reason);

14- Limited mental capacity or psychiatric disease rendering the subject unable to provide written informed consent or comply 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.

9.3 Concomitant treatments

A concomitant medication is any treatment received by the patient concomitantly to the study drug during the study. All concomitant treatment have to be recorded in the case report form (CRF) with the following information: name, dosage, route of administration, dates of intake.

9.3.1 Authorized concomitant treatments

PXT3003 will be administered on top of standard of care (SOC) consisting of supportive therapies such as pain killers (except neurotoxic drugs or opiates), physiotherapy, occupational therapy, and orthopedic devices that will be authorized during the entire study.

All concomitant treatment should be reported in the CRF.

9.3.2 Forbidden concomitant treatments

The following concomitant treatments are forbidden within 30 days before randomization and during the whole study:

- High doses of Ascorbic acid (≥1 g/day)
- Levothyroxin are forbidden.
- Baclofen, naltrexone, and sorbitol in their current pharmaceutical forms at full dose are forbidden.

The use of opiates, such as morphine, fentanyl, oxycodone, buprenorphine, nalbuphine, tramadol, and methadone potentially neurotoxic drugs should also be avoided. A list of non-recommended treatments is provided in Appendix 1.

9.4 Patient selection and diagnosis of CMT1A

Medical history must include the genetic diagnosis of CMT1A: *PMP22* duplication on chromosome 17p11.2, and disease duration with symptoms progression since less than 15 years.
Demographic data including age, height, weight, gender will be obtained for each patient screened for entry into the study.
The severity of CMT1A will be assessed using the CMTNS-v2 score which should be >2 and ≤18, and the nerve conduction slowing assessed by electrography should be > 15m/sec.

10. INVESTIGATIONAL TREATMENT

10.1 Description of the study treatment and dosage regimen

The tested active drug PXT3003 is a fixed dose combination of RS-baclofen, naltrexone hydrochloride and D-sorbitol.

Two active doses will be tested, compared to placebo of PXT3003:

- Dose 1: 3 mg baclofen, 0.35mg naltrexone and 105 mg sorbitol) given twice per day
- Dose 2: 6 mg baclofen, 0.70mg naltrexone and 210 mg sorbitol) given twice per day

Qualitative and quantitative composition of the PXT3003 clinical formulations:

	Dose 1	**Dose 2**
D-sorbitol	21 mg/ml	42 mg/ml
Naltrexone HCl	0.07 mg/ml	0.14 mg/ml
(RS)-baclofen	0.6 mg/ml	1.2 mg/ml

List of excipients: acetate buffer, Na methyl paraben, Na propyl paraben and 2-methylbutyl acetate (banana flavour).

The dosage regimen will be 5 ml per intake twice daily.

Each strength (corresponding to dose 1 and dose 2) of the tested drug PXT3003 and its matching placebo will have the same presentation, the same aspect and taste in order to be undistinguishable, and they will be supplied and used in a similar condition.

They will be supplied in **amber glass bottles containing 100ml of clear oral solution**. Each bottle will be delivered with a plastic adapter (already inserted in the bottle neck) and an adaptable plastic pipette for medication dispensation. The **pipette will be graduated with a 5 ml graduation corresponding to the full dose and 2.5 mL for the half-dose of medication to be administered**. Each bottle will contain a volume of medication corresponding to 10 days of treatment. The study medication will be provided in carton boxes of 4 bottles (with 4 pipettes) for one month.

Treatment shall be taken orally twice a day with food (in the morning with the breakfast and in the evening with the dinner) during 15 months.

To improve treatment tolerability at the highest dose, treatment should start progressively (for all randomized patients): **half dose (2.5ml of the liquid formulation) will be administered twice a day during the 2 first weeks** and will then be increased to the full dose (5ml of the liquid formulation) twice a day until the end of study treatment.

Patients randomized to PXT3003 will be supplied with the appropriate number of disposable glass bottles and carton boxes specifically labelled for the use in the study where required by local regulation. These will be dispensed at baseline, and every three months (e.g. 3 carton boxes of 4 bottles for 3 months).

10.2 Treatment packaging and labelling

Study treatments (PXT3003 and placebo) will be manufactured by Quay Pharma (UK), then after importation in France, packed, labelled/certified for clinical trial use, and shipped by Theradis Pharma (France) to the sites pharmacies in accordance with applicable regulations, e.g. with the current GMP guidelines, ICH Guidelines Good Clinical Practice (ICH E6), and with the local laws and regulations.

Study treatments (PXT3003 and matching placebo) will be **provided in carton boxes of 4 bottles of 100ml solution for 1 month.**

Study treatments will be numbered according to a material randomization list, separate from the subject randomization list. Blinding will be ensured.

Labelling will comply with applicable rules and regulations. The study treatment will be labelled with the following information (in local language):

- Name, address and telephone number of sponsor
- Pharmaceutical dosage form
- Route of administration
- Quantity of dosage units
- Batch and/or code number to identify the contents and packaging operation
- A trial reference code allowing identification of the trial
- Treatment number
- Directions for use
- Specific mention "For clinical trial use only"
- Storage conditions
- Expiry date

10.3 Management of study treatment

Study treatments (PXT3003 and placebo) will be supplied by Theradis Pharma, France. Treatments will be shipped to the pharmacy at the Investigator's site.

The pharmacist or investigator will be provided with all the necessary documents required concerning information on PXT3003, according to the Good Clinic Practice (GCP) (ICH topic E6 and local regulations). The hospital pharmacist or investigator will be responsible for the correct storage and handling of the study products (reception, storage, dispensation log, update of the delivery list, return of empty packaging and unused units and return of study treatment to the sponsor). As soon as treatment units are received on site, the pharmacist or investigator will return the enclosed acknowledgement of receipt sheet to a PHARNEXT representative which is filled-in and signed. Study treatments under the pharmacist's or investigator's responsibility have to be stored in a secure limited access area, in accordance with required storage conditions, and their whereabouts disclosed only to persons authorised to have access to this storage room.

In accordance with GCP regulations (ICH topic E6 and local regulations) all study materials (unused treatment units, packaging) have to be returned by the pharmacy to the PHARNEXT supplier at the end of the study. The attestation of return will indicate for each patient:

- date of study treatment reception and quantity,
- number of administered and unused therapeutic units,
- number of undelivered units,
- number of therapeutic units finally returned and dispatch date.

In case of a therapeutic unit loss, the investigator or the hospital's Pharmacist in charge of the treatment management will have to justify this loss in a written statement, signed and dated and enclosed with the attestation of return.

The unused therapeutic units will be retrieved by the supplier at the end of the study (i.e. after the final study report signature) and after the reconciliation of the dispensation log of the therapeutic units.

10.4 Storage

All study drugs must be stored in a locked storage facility to which only the investigator, pharmacist or designated assistants will have access.

The study drugs should be stored in a refrigerator at controlled temperature between +2°C and +8°C.

The shelf-life for PXT3003 is 36 months in refrigerated conditions (+2 to +8°C).

However the data generated so far support **transportation at ambient temperature**: in order to handle

shipping conditions, stability studies were conducted at +25°C 60%RH and 30°C 65%RH and no degradation was seen within at least 6 months. Thus **excursions at ambient temperature (<30°C) are tolerated for a total time of no more than 30 days.**

Once opened, PXT3003 **bottles must be kept in a refrigerator at a temperature of +2°C to +8°C and can be used for up to 10 days**.

10.5 Dispensing and drug accountability

The study treatment will be dispensed only under restricted conditions as defined in the present protocol. Once the eligibility of the patient is confirmed by the investigator (all inclusion and exclusion criteria checked), **patients will be assigned a randomization number** according to the randomization process in the interactive web randomization system (**IWRS**) and dispensed a corresponding study drug kit.

The treatment will be dispensed only by the investigator under his/hers direct supervision or the pharmacist. Adequate records on receipt, dispensation, initials of the person dispensing the drug, use, return, loss, or other disposition of medication must be maintained. These records include dates, quantities, batch numbers, expiration dates, subject identification (initials) and the unique code numbers assigned to the study patients.

Patients will receive at each visit the necessary quantity of treatment until the subsequent one (including extra bottle(s) to cover for a potential delay [+/- one week] in study visits or any problem of study drug conservation). This will correspond to **3 boxes of 4 bottles of PXT3003 every 3 months**. The actual boxes to be dispensed will be **assigned by the IWRS**. Treatment should be taken until the last visit (at 15 months).

Study drugs must only be used for the study purpose and must not be used outside this protocol.

Patients should return empty and partially emptied or unused bottles to the hospital at each visit to receive (a) new kit(s).

At each visit the compliance/adherence to the treatment will be investigated: details of the quantities of bottles of medication dispensed and the count of used bottles returned will be recorded at each visit to report the compliance.

The patients will be asked whether the investigational treatment was taken as prescribed. If not, any change in the treatment and the number of forgotten intakes will be recorded. In addition, the number of quantities will be counted and compared to the theoretical quantities. Any mismatch will be investigated and justified in collaboration with the patient if possible.

Patients should be **instructed to store study medication in the refrigerator** (both unused and opened bottles). **However, transportation from the investigator's site to the patient's home can be done at ambient temperature (<30°C)**.

During use, **opened bottles** containing the study medication will be **stored in a refrigerator for a maximum duration of 10 days. Freezing must be avoided:** It necessary to avoid storing carton boxes or glass bottles against the walls of the refrigerator.

The storage conditions in the refrigerator does not allow to include several patients of the same family under the same roof and using the same refrigerator, which justifies the exclusion criterion No. 15 in order to avoid the risk that patients invert their processing boxes corresponding to each blind treatment which would jeopardize the interpretation of the study results.

If a patient from the same family, living in the same household, has already been included in the same study, it is not possible to accept the patient to avoid mixing of therapeutic units and therefore there would be a risk of inversion of the blind treatments.

11. CONDUCT OF THE STUDY

11.1 Visit schedule

The visit schedule and procedure assessments are listed in the study flow chart in section 3.

This is an outpatient study. Usually CMT1A patients come to visit their specialist annually and many of them may live far from the reference center, so the number of visits is limited.

The study will be conducted on a **total of 15 months** with evaluations visits at baseline (screening and randomization visit), 6 months, 12 months and 15 months.

Intermediate visits are scheduled at 3 months and 9 months for drug dispensation and checking safety (AEs) and treatment compliance. Eventually if local regulations allow that the dispensing of medication can be organized by shipping, these intermediate visits at 3 months and 9 months may be made by phone call.

Visits are scheduled as following:

- V0 - Screening visit: Day-1 to Day -30 max
- V1 - Randomization visit: at Day 0
- V2 - 3-month visit (or telephone call): at Day 90 ± 8 Days
- V3 - 6-month visit: at Day 180 ± 10 Days
- V4 - 9-month visit (or telephone call): at Day 270 ± 10 Days
- V5 - 12-month visit: at Day 360 ± 10 Days
- V6 - 15-month visit: at Day 450 ± 10 Days

If one visit date is changed (anticipated or delayed), the next visit should occur according to the original schedule.

All visits must be performed by investigators and sub-investigators qualified for this study and who are expert in the management of CMT1A patients.

11.2 Study procedures at each visits

11.2.1 Screening period

The duration of the screening period is up to 4 weeks and must be long enough to establish inclusion/exclusion criteria: from visit 0 (between day-1 and day -30 max) to the inclusion visit (i.e. visit 1 at day 0).

Electrophysiological testing to assess CMTNS score, blood tests (haematology and chemistry) and ECG for safety will not be re-assessed at randomization (visit 1) if they are performed at screening (visit 0) within the previous 14 days. If time between V0 and V1 is greater than 14 days, they must be repeated at randomization to assess baseline.

The following procedures/assessments will be performed at the screening period within 30 days prior to inclusion:

- **Obtaining the informed consent**

Patients who meet all inclusion and none of the exclusion criteria will be informed about the study. If a patient is eligible to be enrolled in the study, the investigator should give to the patient the study's informed consent form and orally present all necessary information to the patient, in order to enable him to make an informed but uncoerced decision about participating in the study. Objectives,

treatments, expected benefits, potential risks, constraints and procedures of the study will be carefully explained to the patient. An adequate delay for the patient to decide if he is willing to participate in this study will be respected. **An appropriately signed informed consent form will be obtained prior to entry into the study** for each patient who has made the decision to participate. It is only after the patient has accepted to be enrolled, that any protocol specific test and examination can be performed.

In case of children 16 to 18 year-old age, both parent's and children's consents should be collected.

- **IVRS/IWRS notification**

The IWRS through eCRF will be used at V0 for notification of screening and patient number allocation. First demographic information and the date of signature of consent form will be collected.

In case of rescreening, a new patient number will be assigned by the IWRS.

In case of screening failure, the site will have to record it via IWRS at V1 (baseline) and to report the reason.

The patient number is composed of a 7-digit number containing the 2-digit country code, the 2-digit center code and the 3-digit patient chronological number (which is 001 for the first patient screened and 300 for the last patient screened).

- **Laboratory testing by the central laboratory**

Safety laboratory tests sampled at V0 and measured at the central laboratory are needed for checking the exclusion criteria. If any of the laboratory parameters are not available upon the end of the screening period (e.g., sample material damaged during transport etc.) a retest can be performed.

- **Assessment of inclusion/exclusion criteria**

The following information must be collected and documented in the CRF within the screening period:

- Patient history of **CMT1A with documented genetic diagnosis** should be noted in the source document;
    - If not already documented, blood sampling (4 ml) for the PMP22 duplication genetic test will be performed.
- Patient history of all the treatments including surgery, physiotherapy and medications must be notified in the source documentation prior randomization (with regimen, duration, and complications and their treatments);
- Demographics characteristics (age, gender, and ethnic origin);
- Physical examination including vital signs (SBP and DBP, heart rate), body height and weight;
- Physical and neurological examinations with the presence of weakness at dorsiflexion;
- Electrophysiological tests of sensory and motor responses of ulnar and radial nerves on the non-dominant side (including CMAP, SNAP, NCV, and DML parameters) will be performed to determine the CMTNS score;
- 12-lead ECG (sent for centralized reading by a cardiologist);
- Results of safety laboratory tests from the central laboratory;
- Authorized and prohibited concomitant medications.

11.2.2 Inclusion visit = Visit 1

At this Visit 1 the investigator must check that the patient meets all the inclusion criteria and none of the exclusion criteria.

The following assessments must be performed:

- physical and neurological examinations including vital signs (SBP and DBP, heart rate),
- clinical scores and functional tests at baseline:
    - CMTNS score to determine severity (electrophysiological testing performed during the screening period can be used. It should be repeated only if time between V0 and V1 is greater than 14 days)
    - ONLS score,
    - 9-Hole Peg Test in the non-dominant hand,
    - Quantified muscular testing (hand grip and foot dorsiflexion on both sides)
    - 10 m Walking test
- quality of life measured by:
    - EuroQol 5-Dimensional Health-related Quality of Life scale (EQ-5D);
    - VAS on self-assessment of the individualized main impairment in daily activities defined at baseline with the patient;
- assessment of any Adverse Event,
- review of concomitant treatments,
- blood sample for PK before dosing,
- blood sample for biomarkers,
- blood sample for safety and ECG should be repeated only if time between V0 and V1 is longer than 14 days,
- skin biopsy (optional /ancillary study),
- leg MRI (optional /ancillary study).

Then the patient will be included in the study and will be assigned a randomization number.

A treatment will be allocated according to the randomization number determined by IWRS; prescription and drug dispensation can be done.

The patient will receive **3 boxes of 4 bottles for the next 3 months**, and will be instructed to **store them in the refrigerator.**

The study medication is an **oral solution** contained in 100 mL bottles which will be delivered with a plastic adapter and an adaptable graduated pipette for medication dispensation. The pipette has 2 graduations: 5 ml for the full dose and 2.5 mL for the half-dose of medication to be administered.

The patient will be **instructed to take the study medication twice daily (one intake in the morning with the breakfast, and one intake in the evening with the diner) by swallowing the contents of the pipette**. **The first 2 weeks, he will take half-dose at each intake corresponding to the 2.5 ml graduation, and then until the end of the study the full dose e.g. 5 ml, twice a day.**

The **first dose will be administered to the patient at the hospital** with a small meal and blood sample will be performed 90 minutes after this first drug intake for PK assessment.

The patient will be instructed to contact the investigator by phone should an adverse event occur, and will be asked to bring back the used and unused investigational treatment packs at the following visit.

11.2.3 Visit 2 at 3 months

The visit at 3 months is essentially for drug dispensation, checking safety (AEs) and treatment

compliance. Eventually, if local regulations allow that the dispensing of medication can be organized by shipping, this intermediate visits at 3 months may be made by phone call.

The investigator has to interview the patient and to detect the occurrence of potential adverse events, or any change in the concomitant treatments.

The patients will be asked whether the investigational treatment was taken as prescribed. If not, any change in the treatment and the number of forgotten intakes will be recorded. In addition, the number of used and unused bottles will be counted and compared to the theoretical quantities that should be used according to the time from last visit. Any mismatch will be investigated and justified in collaboration with the patient if possible.

11.2.4 Visit 3 at 6 months

The following assessments must be performed:

- physical and neurological examination including vital signs (SBP and DBP, heart rate),
- electrophysiology testing of sensory and motor responses of ulnar and radial nerves on the non-dominant side, including CMAP, SNAP, NCV, and DML parameters.
- clinical scores and functional tests will be assessed:
    - ONLS score
    - CMTNS score
    - 9-Hole Peg Test in non-dominant limb
    - Quantified muscular testing (hand grip and foot dorsiflexion on both sides)
    - 10 m Walking test
- quality of life measured by:
    - EuroQol 5-Dimensional Health-related Quality of Life scale (EQ-5D);
    - VAS on self-assessment of the individualized main impairment in daily activities defined at baseline with the patient;
- review of concomitant treatments
- review of Adverse Events
- blood sample for biomarkers
- blood samples for PK (one before dosing, and one 90 minutes after drug intake)
- blood sample for safety
- review of compliance to study drug and drug accountability: the patient will be asked whether the investigational treatment was taken as prescribed. If not, any change in the treatment and the number of forgotten intakes will be recorded. In addition, the number of used and unused bottles will be counted and compared to the theoretical quantities that should be used according to the time from last visit. Any mismatch will be investigated and justified in collaboration with the patient if possible.

11.2.5 Visit 4 at 9 months

The visit at 9 months is essentially for drug dispensation and checking safety (AEs) and treatment compliance. Eventually if local regulations allow that the dispensing of medication can be organized by shipping, these intermediate visits at 3 months may be made by phone call.

The investigator has to interview the patient and to detect the occurrence of potential adverse event, or

any change in the concomitant treatments.

The patients will be asked whether the investigational treatment was taken as prescribed. If not, any change in the treatment and the number of forgotten intakes will be recorded. In addition, the number of used and unused bottles will be counted and compared to the theoretical quantities that should be used according to the time from last visit. Any mismatch will be investigated and justified in collaboration with the patient if possible.

11.2.6 Visit 5 at 12 months

The following assessments must be performed:

- physical and neurological examination including vital signs (SBP and DBP, heart rate),
- electrophysiology testing of sensory and motor responses of ulnar and radial nerves on the non-dominant side, including CMAP, SNAP, NCV, and DML parameters.
- clinical scores and functional tests will be assessed:
    - CMTNS score
    - ONLS score
    - 9-Hole Peg Test in non-dominant limb
    - quantified muscular testing (hand grip and foot dorsiflexion on both sides)
    - 10 m Walking test
- Quality of life measured by:
    - EuroQol 5-Dimensional Health-related Quality of Life scale (EQ-5D);
    - VAS on self-assessment of the individualized main impairment in daily activities defined at baseline with the patient;
- review of concomitant treatments
- review of Adverse Events
- blood sample for biomarkers
- blood samples for PK (one before dosing, and one 90 minutes after drug intake)
- blood sample for safety
- review of compliance to study drug and drug accountability

11.2.7 Visit 6 at 15 months

The following assessments must be performed:

- physical and neurological examination including vital signs (SBP and DBP, heart rate),
- electrophysiology testing of sensory and motor responses of ulnar and radial nerves on the non-dominant side, including CMAP, SNAP, NCV, and DML parameters.
- clinical scores and functional tests will be assessed:
    - CMTNS score
    - ONLS score
    - 9-Hole Peg Test in non-dominant limb
    - quantified muscular testing (hand grip and foot dorsiflexion on both sides)
    - 10 m Walking test
- quality of life measured by:
    - EuroQol 5-Dimensional Health-related Quality of Life scale (EQ-5D);

- VAS on self-assessment of the individualized main impairment in daily activities defined at baseline with the patient;

- review of concomitant treatments,
- review of Adverse Events,
- blood sample for biomarkers,
- blood samples for PK (one before dosing, and one 90 minutes after drug intake)
    - Attention: PK samples are not applicable in the dose 2 arm if the end of study visit is performed due to discontinuation of the dose 2 arm.
- blood sample for safety,
- 12-lead ECG (sent for centralized reading by a cardiologist);
- skin biopsy (optional /ancillary study),
- leg MRI (optional /ancillary study),
- review of compliance to study drug and drug accountability

11.3 Subject withdrawal

In accordance with the Declaration of Helsinki, patients will be free to withdraw from the study at any time if they wish to do so, for any reason specified or unspecified.

Before the final scheduled study visit, the investigator has the responsibility and the right to end patient participation in the study. For non-emergency situations, listed below, the investigator is required to contact the sponsor or their representative before implementing his/her decision.

11.4 Criteria for subject withdrawal from the trial

Patient may be withdrawn from the study in the following circumstances:

- voluntary withdrawal of patient consent, loss of follow-up or patient inability to remain under medical observation,
- non-compliance or major deviation from the protocol,
- deterioration of patient's condition which no longer enables him/her to comply with the protocol,
- Appearance of a Serious Adverse Event (SAE) or any other situation where, in the opinion of the investigator, continuation in the study would not be in the best interests of the subject.

Should any of the subjects be withdrawn from the study then the reason(s) for withdrawal must be recorded in the e-CRF and in the patient's medical records.

11.5 Follow-up for withdrawn patients

When a subject is prematurely withdrawn from the study, before *V6 at 15 months,* the investigator must perform a complete *"end of study visit"* (as soon as possible) after patient withdrawal.

The Investigator must make every effort to contact patients lost to follow-up. Attempts to contact such patients must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter). Particularly, effort must be done to obtain data on patient's health status (death: yes/no) and to determine the reason why he/she failed to attend the visit. If death occurs, a death certificate will be collected by the investigator.

11.6 Study discontinuation

11.6.1 Criteria for terminating the trial

Pharnext reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. In all cases the Ethics Committee (IRB/IEC) and Health Authorities should be informed. Possible reasons for the study termination can include, but are not limited to;

- the discovery of an unexpected, significant or unacceptable risk to patients enrolled in the study
- a decision on the part of Pharnext to suspend or discontinue the development of the investigational product
- request by the relevant regulatory agency
- decision of the DSMB

If the study is prematurely discontinued then enrolled patients should be called for an "end of study visit"

11.6.2 Criteria for terminating a site

Pharnext reserves the right to terminate the study at a given site at any time after the study initiation should any of the followings occur:

- ICH GCP regulations have not been observed,
- the protocol has been violated without justification,
- the data generated are of poor quality,
- changes in personnel or facilities adversely affect performance of the study (e.g. low rate of inclusion).

11.7 Follow up extension study

At the end of the study, patients having completed the study will be eligible to receive PXT3003 in a **9-month follow-up extension trial**, since upon the investigator's judgement they are likely to benefit from use of the medication and if they are willing to prolong their participation in the trial.

The follow-up study will be defined by a **separate protocol**, a new information about this second study will be delivered to the patient, and he will have to provide a new written informed consent.

All the patients randomized to Dose1 or Dose 2 of PXT3003 in this primary study will continue the extension study at the same dose, while patients receiving placebo will be assigned to one of the two doses according to 1:1 randomization. Thus all patients will receive active study drug for 9 extra months in double blind.

First, this extension study will stimulate the recruitment in the primary 15-month study by encouraging patients to be enrolled if they can benefit from active treatment.

Second, it will provide additional long-term data (up to 2 years) on safety and efficacy in double blind design with delayed start for placebo group switched to active dosages of PXT3003 that may provide some evidence of disease modifying effect.

From V1.4: adapted section as follows

Patients who completed this 15-month study or who were prematurely discontinued from the PXT3003 dose 2 administration will be offered to enter the open-label extension study CLN-PXT3003-03.

Patients previously assigned to dose 2 PXT3003 will receive the equivalent of dose 2 (i.e. 5 mL per administration), by use of its equivalent dose, i.e. twice the dose 1 PXT3003 (2x5 mL, i.e. 10 mL per administration) in the study CLN-PXT3003-03.

Patients previously assigned to dose 1 PXT3003 or placebo and who have completed the pivotal phase III study will receive dose 1 PXT3003 (5 mL) in the study CLN-PXT3003-03.
Hence the protocol of extension study has been amended to assign all placebo patients to dose 1 IMP only, whereas patients previously assigned to dose 1 IMP will continue to do so. As a consequence of the difference of IMP volume (i.e. 5 mL and 10 mL) to be administered the study has become an open-label study that no longer randomizes patients to study treatment.

12. SAFETY ASSESSMENTS AND REPORTING

12.1 Adverse Events

12.1.1 Definitions

12.1.1.1 Adverse Events (AEs)

The term **Adverse Event** covers any sign, symptom, syndrome, or illness which appears or worsens in a patient during the observation period of the clinical study and which may impact upon the patient's well-being.

The AE reporting period therefore starts with the patient signing the Informed Consent Form and ends one month after the last administration of study drug. Events occurring during the drug-free and pre- and post-treatment periods should also be designated as adverse events.

The term also covers laboratory findings or results of other diagnostic procedures which are considered to be clinically relevant (e.g, that require unscheduled diagnostic procedures or/and treatment measures or result in withdrawal from the study).

An adverse event may be:

- a new illness,
- the worsening of a sign or symptom of the condition under treatment or of a concomitant illness,
- an effect of the study medication,
- a combination of two or more of these factors.

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "Adverse Event."

Vital signs and ECG abnormalities, abnormal laboratory values, showing significant shifts from baseline that the investigator considers to be clinically significant, have to be reported as Adverse Event (If there are symptomatic and/or requiring either corrective treatment or consultation, and/or leading to IMP discontinuation or modification of dosing, or fulfilling a seriousness criteria).

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition, for which surgery is required, may be an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the patient signs the informed consent. In the latter case, the condition should be reported as medical history.

12.1.1.2 Treatment Emergent Adverse Events (TEAEs)

A treatment-emergent adverse event is defined as any event not present prior to the initiation of the study treatment, or any event already present which worsens either in intensity or frequency following the exposure to the study treatment.

12.1.1.3 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening[1],
- requires patient's hospitalization or prolongation of existing hospitalization[2],
- results in persistent or significant disability/incapacity[3],
- is a congenital anomaly/birth defect;
- is medically important[4].

[1] **"Life-threatening"** means that the patient is at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it was more severe.

[2] '**Hospitalization**' is defined as inpatient care that covers more than one calendar day.

[3] **"Persistent or significant disability or incapacity"** means that there is a substantial disruption of a person's ability to carry out normal life functions.

[4] **Medical** and scientific judgment should be exercised in deciding whether adverse events may be considered serious because they jeopardize the patient, or may require intervention to prevent one of the other outcomes listed in the definition above. The list of critical terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List) should be used as guidance for adverse events that may be considered serious because they are medically important.

Cases involving cancer as an Adverse Event should be reported as "serious" using the criterion "medically important" if no other serious criterion is met.

12.1.1.4 SAE waived from expedited regulatory reporting to regulatory authorities

For the purpose of the study the following events will not be designated as a serious adverse event (SAE):

- hospital admission as a part of the normal planned treatment or monitoring of the studied indication and not associated with any deterioration in condition,
- hospitalization or prolongation of hospitalization planned before inclusion in the study,
- admission for diagnostic evaluation of an AE,
- overnight hospitalization due to social or travel reasons.

12.1.1.5 Clarification of the difference in meaning between "severe" and "serious"

The terms "severe" and "serious" are not synonymous:

- **"serious"** is **based on patient/event outcome** or action criteria usually associated with events that pose a threat to a patient's life or functioning. "Seriousness" (not severity) serves as a guide for defining regulatory reporting obligations.
- **"severe"** is used to **describe the severity** e.g. intensity of a specific event, which could be rated ***mild, moderate or severe***. The event itself, however, may be of relatively minor medical significance (such as severe headache).

12.1.2 Guidelines for reporting Adverse Events

All AEs, whether or not considered by the investigator to be related to the study drug, must be **recorded in the patient's medical records and in the CRF**. For each adverse event, the reported term, onset and end dates, severity, consequences on study drug intake (action taken), relationship to study drug, outcome and information on seriousness of the event will be recorded.

The severity, the relationship to the study drug and the outcome of the adverse event will be assessed by the investigator.

- The **severity** (intensity) of each AE must be assessed according to the following classification:

  - Mild: does not interfere with routine activities,

  - Moderate: interferes with routine activities,

  - Severe: patient is unable to perform routine activities.

- The **relationship** of any adverse effect to the study drug must be assessed according to the following rating:

  - Unrelated /unlikely: clearly and incontrovertibly due only to extraneous causes and does not meet criteria listed under possibly or likely related.

  - Possibly / probably related: follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

  - Related: clearly related to the investigational agent or the studied procedure, i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, which can be confirmed by an improvement upon stopping the Investigational Product and reappearance of the event after rechallenge and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- The **outcome** of each AE must be assessed according to the following classification:

  - Ongoing*: the AE has not resolved,

  - **Recovering:** improvement in the patient's condition has occurred, but the patient still has some residual effects,

  - Recovered without sequelae: the patient has fully recovered with no observable residual effects,

  - Recovered with sequelae **: the AE has resulted in a permanent impairment

  - Death: the patient died due to the AE,

  - Unknown: the outcome of the AE is not known because the patient did not return for follow-up (lost to follow-up),

* If an AE is still on-going at the last visit, the patient must be followed up until the outcome can be documented without using "on-going" in the assessment.

* * A description of sequelae must be provided in the e-CRF

In order to ensure the safety of the patients, the investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team as it may be asked by the sponsor.

12.1.3 Guidelines for reporting Serious Adverse Events

All **Serious Adverse Events**, whether or not deemed drug-related or expected, **must be notified immediately or within 24 hours)** of becoming aware of the event to the global pharmacovigilance representatives of the sponsor. The investigator must inform the site monitor. The initial notification must be followed within **additional 24 hours by a written report**, **using the study specific SAE Report Form**, providing all available information and detailed narrative description. Any medically relevant follow-up information must be reported within the same timelines.

After the initial report, the SAE should be promptly described in a detailed written report including all data allowing the event to be documented and using only the anonymous copies (with only the subject identification code: treatment number and initials) from hospitalisation reports and additional performed examination(s). The investigator should also report all elements concerning the follow-up of the SAE.

When reporting a death, the investigator should supply any additional requested information such as autopsy reports (if available) and final medical reports.

The **"Serious Adverse Event" form** and the instructions on completion are provided in the investigator's study file. The "Instructions for Completing the SAE Form" give more detailed guidance on the reporting of SAEs, significant overdose cases, and AEs initially reported as non-serious which become serious.

The Global Pharmacovigilance Representative of the Sponsor will forward any SAE initial and/or follow-up notification/report to Pharnext to the attention of the Chief Medical Officer within one working day, and will also ensure compliance with all regulatory reporting requirements and notify the authorities, ethics committees and investigators as appropriate. All safety reporting responsibilities, timelines and procedures will be in detail described in study specific Safety Management Plan.

12.1.4 Follow-up of Adverse Events

Patients experiencing adverse events will be monitored with relevant clinical assessments and laboratory tests prescribed by the treating physician. The investigator will ensure that follow-up includes any supplemental investigations that might be necessary to investigate the nature and/or causality of the AE/SAE.

All adverse events (including SAEs) must be followed until satisfactory resolution or stabilization.

Any measure taken and follow-up result must be recorded in the patient's CRF, as well as in the patient's source document. Follow-up laboratory results should be filed with the patient's source documentation.

12.2 Vital signs

Vital signs including systolic and diastolic blood pressures (measured in supine position after 10 minutes rest) and heart rate will be measured at each visit. Body weight will be measured only at the screening. Measurements will be recorded in the e-CRF.

12.3 Physical examination

A complete physical examination will be performed at the screening visit (V0) and at each visit for the purpose of observing the patient's overall appearance, general health and behaviour. The examination includes cardiovascular, respiratory, abdominal, neurological, locomotive and dermatologic systems. Any significant abnormalities should be recorded in the eCRF.

12.4 Electrocardiogram (ECG)

An ECG will be performed at the screening visit (V0) and at the end of the single blind treatment (V6 or at early withdrawal visit) using the internationally recognised 12-lead ECG recording which includes date, time, initials of the technician/nurse, initials of the investigator or their deputy, at least 2 complexes for each lead and a single lead run. The corresponding source data will consist of the Cardiograph paper print-outs that should be kept in the file and a copy should be provided to Pharnext (sent to centralized reading center). Main ECG parameters including heart rate, sinusal rhythm PR, QRS, QT and QTc interval will be analysed by a cardiologist in the central reading center.

12.5 Laboratory tests

A full laboratory test should be performed at screening visit (V0), at 6-month (V3), 12-month (V5) and 15-month (V6) visits, or at early withdrawal visit.

The following blood parameters should be evaluated:

- **hematology**: red blood cell count, hemoglobin, hematocrit, platelet count (absolute), white blood cell count and white blood cell count differential
- **biochemistry tests** (serum/plasma): Sodium (Na), Potassium (K), Chloride (Cl), Gamma-glutamyl-transpeptidase (γGT), Alanine aminotransferase (ALAT), Aspartate aminotransferase (ASAT), Alkaline phosphatases, Urea, Creatinine, Total Bilirubin and Blood glucose.

Standard blood tests (including pregnancy test at screening and last treatment visit) will require **12 ml of blood at each sampling** (screening, 3 months, 6 months, 12 months and final follow-up visit (see Study Flow chart).

Laboratory examinations will not be repeated at the inclusion visit if already performed at screening within 14 days.

Follow-up of laboratory test abnormalities:

The subject's best interests will always be the first priority, before those of the trial. Abnormalities of any laboratory tests considered to represent a significant danger to the subject will lead to immediate discontinuation of the drug and the study monitor and sponsor must be informed immediately.

In the event of abnormalities considered not to represent a danger, continuation of the drug can be allowed after a discussion with the study monitor. These subjects will be followed-up by an appropriate medical management until they return to normal or baseline values or if a clinical diagnosis of an undercurrent illness is confirmed. The results of all known laboratory tests required by the protocol will be held / recorded in the subject's e-CRF. All clinically important and abnormal laboratory tests which occur during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator and the study monitor.

12.6 Pregnancies

A **pregnancy test** will be performed at screening and at the end of treatment for all women of child

bearing potential. During all the study, these women should use highly effective method of birth control. Study participants who become pregnant during the study must be withdrawn.

Every newly diagnosed pregnancy of a study subject has to be reported via a **'Pregnancy Re-port Form'** which must be submitted within 24 hours of learning of its occurrence to the Global Pharmacovigilance Representative of the Sponsor. A newly diagnosed pregnancy in a patient that has received a trial medication is not considered a serious AE, unless meeting any criteria of seriousness or if it is suspected that the trial medication interacted with a contraceptive method and led to the pregnancy.

The pregnancy must be followed up to determine outcome, including spontaneous abortion or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and new-born complications. Every infant has to be followed for 2 months after delivery.

13. OTHER EXPLORATORY ASSESSMENTS

13.1 Plasma level of PXT3003 components

Blood sampling for PK (around 5 mL twice) will be performed before drug administration (trough) and 90 minutes after (peak) at baseline (V1), and at 6-month (V3), 12-month (V5) and 15-month (V6) visits. Pharmacokinetic analysis will require **10 ml of blood to be withdrawn at each point.**

Peak and trough levels of baclofen, naltrexone and 6ß-naltrexol will be measured using a validated LC-MS/MS method developed by Bertin Pharma, France.

Sorbitol will not be dosed for technical reasons: first it is a natural sugar and it is difficult to discriminate between plasma levels of PXT3003-derived sorbitol and sorbitol from other (e.g. dietary) origins, and second after IV injection D-sorbitol plasma levels are measurable for only 10 minutes.

Complete information on blood sampling, conditions of preparation and storage (-80°C) as well as shipment details for PK and Central laboratory contact details will be supplied in a separate technical brochure provided by the central laboratory.

13.2 Blood Biomarkers gene expression analyses and DNA sequencing

Blood sampling for biomarkers (around 10mL) will be performed at the inclusion (V1) and at 6-month (V3), 12-month (V5) and 15-month (V6) visits for a total of 15 ml each time.

Five potential blood biomarkers have been selected (tryptophan, alanin, serotonin, T4 and free cholesterol), first through a pilot study exploring the differences in the expression of potential biochemical markers in Transgenic PMP22 rats versus Wild Type Sprague Dawley rats. The phase II conducted in humans provided confirmation of the interest of these biomarkers, particularly tryptophan, alanine and free cholesterol. Moreover other markers could be assessed for quantification studies, and thus identified later after the accomplishment of this clinical trial.

An additional blood sample (5mL) will be drawn at the inclusion visit only to collect leucocytes in order to realize DNA sequencing for research purposes.

Complete information on blood sampling, conditions of preparation and storage (-80°C) as well as shipment details for these samples will be supplied in a separate technical brochure.

13.3 Skin biopsy (optional ancillary sub-study)

Some investigating site will perform skin biopsies. A specific processing protocol will be provided.

Skin biopsy is a minimally invasive procedure that is used mainly in the evaluation of non-myelinated nerve fibres in sensory neuropathies. Recent data suggested that skin biopsy may replace, under certain circumstances, the more invasive sural nerve biopsy in the morphological and molecular evaluation of inherited and other demyelinating neuropathies (Li, Bai *et al*., 2005; Katona, Wu *et al*., 2009; Saporta, Katona *et al.,* 2009).

A skin biopsy consisting in one small punch biopsy (3 mm of diameter) at the lateral calf 10 cm above the lateral malleolus will be performed before treatment at baseline (V1) and after treatment (V6) to all patients randomized in the site that are engaged in this sub-study . This will allow to assess mRNA levels of PMP22 and other putative candidates biomarkers as exploratory pharmacodynamic endpoints of the present study. Complete information on sampling, conditions of preparation and storage as well as shipment details and laboratory contact details will be supplied in a separate technical brochure.

13.4 Leg MRI (optional ancillary sub-study)

Some investigating sites will participate in an optional ancillary sub-study leg MRI for research purpose on potential new imaging biomarkers. Legs MRI will be conducted at Baseline and the end of the study. A specific processing protocol will be provided separately to ensure the standardisation of the MRI acquisition across all sites, and centralized reading will be organized.

14. STATISTICAL CONSIDERATIONS

14.1 Analysis sets

The **Full Analysis Set (FAS)** will be constituted by all the randomized patients.

The **Per-Protocol (PP)** population will include all the patients of the FAS without major protocol violation during the course of the study.

All the efficacy analyses will be conducted on the FAS population and reproduced on the PP population for sensitivity purposes. The safety analyses will be conducted on the FAS, given that all randomized patients will receive at least one dose of treatment.

14.2 Primary efficacy analysis

The significance of the studied drug effect compared with Placebo will be tested by an Analysis of Covariance (ANCOVA) on the summary mean of ONLS at 12 and 15 months adjusted for baseline ONLS values. ANCOVA will be featured by a Linear Mixed Model (LMM), including baseline ONLS values and treatment as fixed factors, and center as random effect. The use of two repeated post-baseline measures increases the power to detect treatment differences in mean levels of the outcome measure over time (Frison and Pocock, 1992; Morgan and Case, 2013).

Two active doses will be compared to Placebo. As the monotonicity of dose effect is not assumed, each dose will be compared at a two-sided 2.5% significance level, in order to preserve an overall false-positive rate of 5%.

14.3 Sample size calculation

Assuming ANCOVA with 2 post-baseline measures, a linear correlation coefficient of ONLS of R = 0.75 between baseline and end of the study, a standard deviation of ONLS of SD ≅ 1, and a negligible between center standard deviation (estimated SD = 0.13 [0;0.35]), the resulting adjusted standard deviation ASD ≅ $[1*(1-.75^2)]^{.5}$ ≅ 0.65, thus a minimum clinically relevant difference in ONLS should be a Cohen's Δ of 0.65/2 ≅ 0.325, rounded to Δ = 0.3. From calculations based on compound symmetry of the covariance matrix (Frison and Pocock, 1992, Morgan and Case, 2013), such a difference should be detected versus Placebo with a power of 90% at a two-sided 2.5% significance level when the sample size reaches at least 89 patients per group. Assuming a drop-out rate of ≅ 10%, we anticipate recruiting 100 patients per group for a total of at least 300 patients.

The parameters needed for sample size calculation were evaluated based on historical trials (Micallef, Attarian *et al.*, 2009; Pareyson, Reilly *et al.*, 2011; Attarian, Vallat *et al.*, 2014).

14.4 Secondary efficacy analyses

The primary ANCOVA analysis based on the summary mean at 12 and 15 months will be repeated on the other quantitative efficacy endpoints (see above). The significance of the treatment effect on each quantitative endpoint will also be evaluated based on the difference compared to Placebo in change from baseline at each individual visit and in slope of progression over the duration of the study. The proportion of responders at 15 months will be assessed through a Generalized Linear Mixed Model (GLMM) featuring logistic regression, and admitting center as a random effect. Secondary analyses will be conducted at a two-sided 5% significance level.

14.5 Missing data

Few missing data were observed in past trials in this pathology. Due to likely expected loss of efficacy after treatment discontinuation, and a possible deterioration compared with baseline values, last or baseline observation carried forward may not be appropriate. Missing values will be imputed using a linear model estimated on the Placebo group. The potential impact of missing data on the study's conclusions will be evaluated. Descriptive data analyses will allow assessing the pattern of missing data, including reasons for drop-outs in each treatment group. In addition, sensitivity analyses will be conducted by using other missing data approaches (further details in the SAP).

For any patient experiencing early trial interruption, an early interruption visit is planned. It will be checked if this visit took place within a given time frame where the next regular visit would have been planned. In case the early interruption visit occurs within this time frame, data of the early interruption visit will be shifted to the next regular visit for all analyses. In case the early interruption visit does not occur within this time frame, the data of the early interruption visit will not be included in any of the inferential analyses.

14.6 Safety analyses

Safety and tolerability will be assessed by summarizing and analyzing adverse events (AEs), change in physical examination, vital signs, electrocardiogram (ECG) and laboratory data.

The incidence of Treatment Emergent Adverse Events (TEAEs), related AEs (including possibly and probably related AEs) with moderate or severe intensity, AEs leading to withdrawal of study drug, and Serious Adverse Events (SAEs) will be summarized by treatment groups. This summary will show

incidence rates (number and percentage of patients) with corresponding 95% confidence intervals. Moreover, 95% confidence intervals for the difference in incidence rates between each group will be calculated.

Changes in physical examination, vital signs (blood pressure and heart rate) and ECG will be analyzed descriptively.

Changes from baseline to the end of the treatment period in laboratory values for hematology and blood chemistry will be summarized descriptively. Each laboratory value will be flagged to show whether it lies within, below, or above the normal range. The proportion of subjects with values in each of these categories at each assessment will be also summarized.

14.7 Data Safety Monitoring Board (DSMB)

An independent DSMB will regularly follow the progress of the clinical trial, monitor safety data and critical efficacy variables, and be consulted concerning the opportunity of modifying the sample size or terminate the trial for futility.

14.8 Adaptive sample size

We based our sample size on the point estimates of the standard deviation (SD) and the correlation between baseline and final values (*R*). Over- or under- estimation is possible due to their wide spread variation. An estimation of the adjusted standard deviation ASD will be performed when 80 patients are available, producing a 95% half interval length of ASD±0.1. In case where the absolute value of the difference between the observed ASD and the value used for initial sample size calculation exceeds 0.1, the sample size will be recalculated. In addition, the drop-out rate of 10% used for sample size calculation will be also updated if its estimation on the first 100 patients is significantly greater and non-related to safety concerns. The adaptive sample size calculation will be organized blind to treatment and do not require any type-I adjustment.

14.9 Futility analysis

A one–stage Futility stopping will be based on Conditional Power, probability to detect a significant result at the end of the study, given the results observed at an intermediate time. Conditional Power (CP) will be estimated through B-values and (Lan and Wittes, 1988; Lan and Zucker, 1993). This analysis will be carried out by a third party statistician when at least 100 patients are available, and futility threshold will be CP_{min} = 0.10 involving a slight increase of type 2 error ($\beta = 0.1/0.9 = 0.111 - 0.10 \cong 0.01$) (Proschan, 1999). This intermediate futility analysis does not require any type-I adjustment, this trial does not plan g rejection of the null hypothesis before its end.

Further details will be described in the Statistical Analysis Plan (SAP) as appropriate.

15. ETHICS AND LEGAL CONSIDERATIONS

15.1 Declaration of Helsinki and conformity with other international standards

The trial will be carried out in accordance with the Declaration of Helsinki (Edinburgh, 2000) completed by notes of clarification to articles 29 (Washington, 2002) and 30 (Tokyo, 2004), respectively, and

revised in 2008 (Seoul) and in 2013 (Fortaleza, Brazil). The trial will also be conducted in compliance with the protocol, the ICH Guidelines for Good Clinical Practice (ICH E6), the European directives on clinical trials (Directive 2001/20/EC) and the applicable local country laws/regulations.

15.2 Ethics Committee / Institutional Review Board Approval

The final study protocol, including the Patient Information and Informed Consent, will be submitted for approval to the appropriate Ethics Committee (EC) or Institutional Review Board (IRB). Any amendment to these documents will be also submitted to the EC/IRB. In case the protocol amendment changes the scope of the study or increases the risks of the study patients, the investigator should wait for approval of this amendment by the EC/IRB before implementing the protocol amendment. A copy of the written approval and the approved versions of the documents and a list of the EC/IRB members, their titles and occupations should be forwarded to the responsible study personnel. The written approval should identify the study and document the date of review. All correspondences with the EC/IRB and forward copies of such correspondence should be provided to the sponsor via the responsible study personnel.

15.3 Emergency actions

The investigator can deviate from the protocol in emergency when it is necessary to safeguard the life or the wellbeing of a study patient. The investigator must give notice of any emergency deviation and justification for the deviation of the study to the personnel responsible for the sponsor and the EC/IRB, as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

15.4 Patient Informed Consent procedure

It is the responsibility of the investigator to give to each patient (or the patient's legally authorized representative) prior to inclusion in the study, full and adequate verbal and written information about the objectives and the procedures of the study, potential risks involved and personal and societal benefits. The patients must be informed about their right to withdraw from the study at any time and for any reason, without sanction, penalty, or loss of benefits to which they are otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. Before deciding on whether or not to participate, the patient should have sufficient time to think about the study and to discuss the study with a third party if necessary. The investigators and their staff will be available to answer questions from the subject at any time. Written information (Patient information and informed consent form) should be given to each patient before enrolment. Furthermore, it is the responsibility of the investigator to obtain, in accordance with the pertinent local regulations, a signed "Informed Consent Form" from each patient (or the patient's legally authorized representative) prior to performing any study-related procedures.

The Patient Information and Informed Consent form should be updated or amended whenever new important information that may be relevant to the patient, becomes available. Modifications to these documents must be approved by the sponsor and by the EC/IRB before being implemented.

15.5 Amending the protocol

Any change to the study must be documented in a protocol amendment. Such protocol amendments will be made jointly by the sponsor and the investigators. Both parties will sign the protocol amendment.

The investigators will submit the protocol amendment for review by the independent EC/IRB if the change or deviation from the original protocol could increase the risks to the studied patients, or could

adversely affect the validity of the investigation, or the rights of the human subjects; they have to obtain approval from the independent EC/IRB before such change(s) or deviation are implemented.

If the change(s) or deviation to the original protocol eliminate or reduce the risk to the study patients, the protocol amendment can be implemented before approval has been received from the independent EC/IRB. In such cases, the investigators will notify the independent EC/IRB within ten working days after implementation and will submit the protocol amendment as soon as possible for information/favourable opinion from the independent EC/IRB.

If the protocol amendment is of the administrative kind, it will be sent to the EC/IRB for information.

16. QUALITY CONTROLE AND QUALITY ASSURANCE

16.1 Direct access to source data/documents

In conformity with GCP (ICH E6), the investigator should provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review and regulatory inspection. Any authorized party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s), to maintain the confidentiality of subject's identities and sponsor's proprietary information.

Each patient should consent in writing to allow direct access to his/her original medical records.

16.2 Monitoring and Good Clinical Practice

The trial will be run in accordance with Good Clinical Practice, following international regulations (ICH) and European directives (EMEA) or national ones.

The sponsor will delegate the monitoring of the study to a contract research organization (CRO). Monitoring will be done by personal visits from a representative of the CRO who will review the case report against source documents and will ensure that the investigation is conducted according to the protocol design, applicable Standard Operating Procedures and regulatory requirements.

At any moment quality control of the study and Good Clinical Practice audit can be performed by the Sponsor or a delegated auditor or by an inspector from an Authority Agency.

In particular, the current protocol will be submitted, by the sponsor, to the Ethics Committee /Institutional Review Board and the Competent Authority, in order to secure their agreements as is required by ICH. The conformity of the study progress will be reviewed.

The investigator will carefully explain the participating conditions to each proposed patient. Each patient will receive a detailed and written information letter which will include the name of the investigational product, a summary of its properties, the potential occurrence of unexpected and adverse events, the doses to be administered, the treatment duration, the number of visits and the type and number of scheduled exams.

The patient will be informed that he can withdraw from the study whenever he/she wants without providing any justification. The investigator will be available by telephone for each patient he/she has included.

The system to attribute treatment numbers to patients respects the obligation of anonymity. Patients will receive a number according to their order of inclusion in the study on a site. The patients will be identified by the sponsor with: the site number and the inclusion number.

Study progress conformity to the protocol will be monitored from the beginning, starting from the patient's selection and continuing throughout the entire study. Each investigator has to allow access to patient's medical file and source documentation (hospitalization file, consultation file, results of additional examinations, etc…) to the monitor, or sponsor's delegated representative, that have to monitor the progress of the study and to check source documents in order to monitor data reported in the CRFs. The anonymity of the patient will be respected when filling-in the CRF along, with any other archived documents considered as source data (blood tests, informed consent form, etc.).

16.3 Monitoring visits

The **monitors (Clinical Research Associates representative of the CRO)** who are delegates of the sponsor will conduct **site initiation visits** at each study site, after approval of the study has been obtained from the independent EC/IRB and Competent Authorities in order to discuss with the investigator the clinical protocol and review data collection procedures, safety monitoring and reporting procedures and regulatory requirements.

Monitoring visits to the study sites will be conducted periodically during the clinical study in order to:

- review the status of the study with respect to patient enrolment, occurrence of adverse events, etc…
- ensure that the clinical investigators continue to respect their contractual, clinical and regulatory obligations with regard to protocol compliance (and compliance to protocol amendments, if applicable), adherence to regulatory and ethical requirements and the protection of the patients' rights and safety,
- ensure the scientific integrity of the study by reviewing the integrity and completeness of the data collected in the CRFs on the basis of the raw data,
- review the completeness and accuracy of the study site records,

Source documents will be reviewed for verification of agreement with data in the CRFs. The study site will guarantee direct access to source documents by designated sponsor personnel or their designees and appropriate regulatory authorities. Monitoring will be conducted according to internal Standard Operating Procedures.

The study may also be subject to a quality insurance audit by the sponsor or its designees, as well as inspection by appropriate regulatory authorities.

It is important that the investigator and the relevant study personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to these processes.

16.4 Investigator qualifications and responsibilities

Investigator should provide a signed and dated copy of his/her current curriculum vitae describing his/her experience, qualification and training prior to the beginning of the study. He should comply with the following conditions:

- Be experienced in neurology, particularly in the management of Charcot Marie Tooth disease and to study procedures/testing facilities adequate for participation in study trial
- Have a sufficient number of CMT1A patients which meet the enrolment goals
- Have previous clinical research experience with training to Good Clinical Practices
- Agree to participate in an appropriate training program if necessary prior to enrolment of first patient

- Be willing to comply with the scheduled follow-up visits as described in the protocol.
- Agree to obtain the patient's Informed Consent before conducting any study-specific tests or procedures
- Be willing to complete all CRFs (e-CRF) promptly, and to answer to any query according to the specificities and guidelines provided by the monitor for using the electronic interface.
- Be willing to spend time to complete the administrative work involved in the study
- Be willing to spend time with the sponsor monitors (Clinical Research Associates) or delegates during the monitoring visits, and to ensure to them direct access to source documents.
- Be willing to change hospital routine if required by the protocol.

The investigator may appoint such other individuals as he/she may deem appropriate as sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All sub-investigators shall be appointed and listed in a timely manner. The sub-investigators will be supervised by and work under the responsibility of the investigator. The investigator will provide them with a copy of the clinical trial protocol and all necessary information.

16.5 Quality control and audit

Audits will be implemented within the framework of the Quality Insurance System to check that the quality requirements of the study are being respected.

The original documents generated in the course of the study will be inspected at each step of the study, both by the sponsor's representative and the investigator, in order to guarantee the accuracy of the analysed data.

The conduct of the study may be audited either by the sponsor or the competent Authorities where the study is performed. Auditors should have access to any study records (CRFs, site files, trial master files, etc.) and source patient's medical documentation, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. Investigators accept the possibility to be audited and agree to dedicate necessary time to the proper conduct of the audit at their sites. This will facilitate the process of ensuring that study is being run in conformity with the protocol and with current rules and regulations.

17. DATA HANDLING

17.1 Data entry in e-CRF

Electronic data capture will be used for the purpose of the study. The e-CRF will be developed and validated by the CRO, representative of the sponsor. The access to the electronic case report form will be provided by the sponsor to the investigator. All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the case report form.

Details of case report form completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the case report form, the names, positions, signatures, and initials of these persons must be supplied to the sponsor.

The investigator, or designated representative, should complete the case report form pages as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed

immediately after the final examination. An explanation should be given for all missing data. According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded in the e-CRF.

A source data location list will be prepared and updated during the study. This list will be filed in both the trial master file and the investigator study file.

The completed case report form must be reviewed and signed by the investigator named in the study protocol. At the end of the study, the sponsor will retain the originals of all case report forms. The investigator will retain a copy of all completed case report form pages.

The informed consent form will include a statement by which the patient allows the sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

It is the responsibility of the investigator to maintain adequate and accurate e-CRFs (according to the technology used), designed by the sponsor to record (according to sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the e-CRF may generate queries to which the Investigator is obliged to respond by confirming or modifying the data questioned. The queries with their responses will be managed through the e-CRF.

17.2 Source data to be recorded in the e-CRF

Source data are all information reported in the e-CRF including certificated copies of original records of clinical findings, observations or other activities in the trial necessary for the reconstruction and evaluation of the trial.

The e-CRF should have the study number, the center number, the patient's study number and the randomization number in the study.

Source data relate to but are not limited to:

Subject demographic data (age, weight, height, and birth's date), general examination, medical history, last participation to a clinical trial if any,

- CMT type 1A genetic diagnosis, history of the disease,
- Current and previous treatments for CMT1A and any other types of treatment,
- Dates and times for drug administration, concomitant medication(s) during the study,
- All data related to efficacy assessment: ONLS, CMTNS, functional tests (QMT, 9-HPT, Walking tests, EQ5D, VAS, electrophysiological parameters),

- All data related to safety assessment: adverse events, vital signs, ECG, results of abnormal values of laboratory tests.

17.3 Record retention

The investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

In order to constitute evidence with respect to product safety or regulatory or legal compliance, the investigators, investigational sites and Ethics Committees agree to retain study related documents in a location that is secure and to which access can be gained if required. The following documents must be archived: the investigator's file containing all required GCP documents, including signed Informed Consent forms and patient-related records, and copy of the e-CRFs. The investigator and the site should **retain records at least 15 years** after the completion or discontinuation of the clinical trial. If the investigator's personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the sponsor and the relevant records shall be transferred to a mutually agreed upon designee. The investigator must notify the sponsor prior to destroy any study essential documents following the clinical trial completion or discontinuation.

These documents must be available for inspection by authorized representative of the sponsor or regulatory authorities. Audits may be performed for quality insurance of data handling.

17.4 Data protection

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the tested product PXT3003.

The patient's personal data, which are included in the sponsor database, shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator and/or to the patients, the sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The sponsor also collects specific data regarding investigator as well as personal data, from any person involved in the study which may be included in the sponsor's databases, shall be treated by both the sponsor and the investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity will be collected in this study. Differences in response to medical products have already been observed in racially and ethnically distinct subgroups of the U.S. population. These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Race and ethnicity information will be collected according to the *FDA Guidance for Industry - Collection of Race and Ethnicity Data in Clinical Trials (2005)*, and in accordance of local laws in the different participating countries.

17.5 Confidentiality and property rights

All documents that concern the studied medication and the company's operations belonging to the sponsor such as patent applications, formulas, manufacturing processes, basic scientific data and analysis bulletins and **any information supplied by the company and not previously published are considered confidential and shall remain the sole property of the sponsor**. The information included in this protocol, along with the investigator's brochure of the product, the e-CRF and the results of the

present study are considered as **confidential and should not be divulged** unless such disclosure is required by law or regulations. The investigator agrees to use this information only in accomplishing this study and they will not use it for other purposes without written consent from the sponsor.

In any event, any persons to whom the information is disclosed such as sub-investigators must be informed that the **information is confidential** and may not be further disclosed by them. **The signature of the present protocol by the investigator is equivalent to a confidentiality agreement.**

It is understood by the investigator that the information from the clinical study will be used by the company in connection with the development of the tested drug and, therefore, may be disclosed as required, to other clinical investigators or to government agencies.

18. REGULATORY ASPECTS

18.1 Financing

The sponsor will cover the additional costs related to this study. These costs will be defined and agreed upon, before the start of the study. A financial agreement will be made between the parties: institution, investigator and sponsor, in accordance with each administrative procedure.

18.2 Insurance

The sponsor will contract a specific insurance policy to insure the patients enrolled in the study, in conformity with the national regulations. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document. The insurance of the sponsor does not relieve the investigator and the collaborators from any obligation to maintain their own liability insurance policy.

18.3 Notification/ application to relevant competent Authorities

According to the individual country law/regulation, the study will not be initiated before it has been approved by the relevant competent Authorities, the Ethics Committee or the institutional Review Board.

19. PUBLICATIONS AND COMMUNICATIONS ON STUDY RESULTS

The sponsor will be responsible for conducting the statistical analysis and for preparing a Clinical Study Report and must provide a summary of study results to the Investigator.

The sponsor will publish the results at the end of the study in an international journal on behalf of the study group including all the principle investigators of all sites, after validation and agreement of the manuscript by the publication committee including the sponsor and the coordinating investigators.

The communication or publication of all or part of the results of this study, including ancillary studies, will be only permitted after written agreement of the sponsor. Any manuscript or presentation should be submitted at least 30 days before submission to the sponsor for review and approval. The objective is to ensure consistency between data submitted to regulatory agencies and data appearing in publications and presentations. In addition, if requested by the sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the sponsor deems appropriate to establish and preserve its proprietary rights. The sponsor has the right at any time to publish the results of the study.

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21.APPENDICES

i. APPENDIX 1- LIST OF NON-RECOMMENDED TREATMENTS FOR CMT1A PATIENTS

- ✓ **Baclofen** (Liorésal®), **naltrexone** (Nalorex®, Revia®) **sorbitol** (pharmaceutical form, such as sorbitol Delalande®, Hépargitol®, Microlax®, Schoum®...) **and ascorbic acid** (vitamin C®, Laroscorbine®...), as they may interfere with study treatment evaluation.
- ✓ **Levothyroxin** (Levothyrox®, L-Thyroxin serb®) as it may confound biomarkers analysis.
- ✓ **Opioid analgesics** (morphine, fentanyl, hydromorphone, oxycodone, buprenorphine, nalbuphine, Lamaline® and tramadol – including Ixprim®, Topalgic®, Contramal® and Zaldiar®) and **other drugs of the opioid class such as methadone** because of their potential interaction with naltrexone.
- ✓ **Codeine** is allowed only at doses of ≤ 20 mg per unit dose; analgesics such as **Efferalgan Codeine®** are therefore not allowed as they contain 30 mg codeine per unit dose.
- ✓ **Levodopa** (Sinemet®, Modopar®, Stalevo®...) should not be used as in combination with baclofen there may be increased adverse effects such as confusion, agitation and hallucinations.
- ✓ **Centrally acting antihypertensive drugs such as clonidine** (Catapressan®), **methyldopa** (Aldomet®), **moxonidine** (Physiotens®), and **rilmenidine** (Hyperium®), as baclofen may increase their antihypertensive effect (risk of hypotension).
- ✓ Other classes of antihypertensive compounds are allowed, but physicians should be aware of a potential increased antihypertensive effect on combined treatment with baclofen.
- ✓ Potent central nervous system (CNS) depressants such as **barbiturates, benzodiazepines, and neuroleptics** are not allowed because of potential increase in side effects in association with baclofen.
- ✓ **Clonazepam** (Rivotril®) can however be used at low daily doses (≤ 20 drops/day, i.e. 2 mg/day).
- ✓ Treatments that may induce or aggravate peripheral neuropathies are also forbidden during the trial, such as the **antiepileptic drug phenytoin** (Di-Hydan®) and anticancer drugs such as **vincristine, vinblastine, cisplatine, carboplatine, oxaliplatine, taxol.**
- ✓ Antiepileptic drugs such as **valproate** (Depakine® or Depakote®), **carbamazepine** (Tegretol®), oxcarbazepine (Trileptal®), **gabapentine** (Neurontin®), **pregabaline** (Lyrica®) can be used but should be maintained at constant doses throughout the trial.
- ✓ **Antidepressant drugs** including **imipraminic antidepressants** can be used, but they should be maintained at constant doses throughout the trial, as imipraminic antidepressant can potentiate the hypotonia induced by baclofen, and sedative antidepressants may potentiate CNS depression.
- ✓ Drugs which could induce neuropathies:
    - Anti-cancer drugs: vincristine, vinblastine, cisplatine, carboplatine, paclitaxel;
    - Anti-infectious: metronidazole, nitrofurantoin, chloramphenicol;
    - Anti-leprosy drug: dapsone;
    - Anti-tuberculosis drug: isoniazid;
    - Anti-retroviral drugs: didanosine (DDI), zalcitabine (DDC);
    - Anti-arythmic drugs: amiodarone;
    - Anti-inflammatory drugs (disease-modifying therapy): gold salts;
    - Alcoholic detoxification: disulfiram;
    - Anti-epileptic drugs: phenitoin;
    - Others: alcohol, pyridoxin(Vit B6) at very high dose;

ii. APPENDIX 2- ONLS

Name:
Date:

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? **Yes** ☐ **No** ☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their bands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0=Normal
1=Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE=____**
2=Disability in one or both arms affecting but not preventing any of the functions listed
3=Disability in one or both arms preventing at least one but not all functions listed
4=Disability in both arms preventing all functions listed but purposeful movement still possible
5=Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐ **If yes:** (please circle) **right/left**	

Leg grade
0=Walking/climbing stairs/running not affected
1=Walking/climbing stairs/running is affected, but gait does not look abnormal **SCORE=____**
2=Walks independently but gait looks abnormal
3=Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4=Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm,frame)
5=Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6=Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7=Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale=arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability)) **TOTAL SCORE=____**
Is there any disorder, other than peripheral neuropathy, which affects the above functions **Yes** ☐ **No** ☐
If **yes** please describe:

iii. APPENDIX 3- CMTNS V2

Table 1. CMT neuropathy score – Version 2.

Parameter	0	1	2	3	4
Sensory symptoms*	None	Symptoms below or at ankle bones	Symptoms up to the distal half of the calf	Symptoms up to the proximal half of the calf, including knee	Symptoms above knee (above the top of the patella)
Motor symptoms (legs)†	None	Trips, catches toes, slaps feet Shoe inserts	Ankle support or stabilization (AFOs) Foot surgery‡	Walking aids (cane, walker)	Wheelchair
Motor symptoms (arms)	None	Mild difficulty with buttons	Severe difficulty or unable to do buttons	Unable to cut most foods	Proximal weakness (affect movements involving the elbow and above)
Pinprick sensibility*,§	Normal	Decreased below or at ankle bones	Decreased up to the distal half of the calf	Decreased up to the proximal half of the calf, including knee	Decreased above knee (above the top of the patella)
Vibration‖	Normal	Reduced at great toe	Reduced at ankle	Reduced at knee (tibial tuberosity)	Absent at knee and ankle
Strength (legs)¶	Normal	4+, 4, or 4− on foot dorsiflexion or plantar flexion	≤3 on foot dorsiflexion or ≤3 on foot plantar flexion	≤3 on foot dorsiflexion and ≤3 on plantar flexion	Proximal weakness
Strength (arms)¶	Normal	4+, 4, or 4− on intrinsic hand muscles**	≤3 on intrinsic hand muscles**	≤5 on wrist extensors	Weak above elbow
Ulnar CMAP (median) Radial SAP amplitude, antidromic testing	≥6 mV (≥4 mV) ≥15 μV	4–5.9 mV (2.8–3.9) 10–14.9 μV	2–3.9 mV (1.2–2.7) 5–9.9 μV	0.1–1.9 mV (0.1–1.1) 1–4.9 μV	Absent (absent) <1 μV

AFO, ankle-foot orthoses; CMAP, compound muscle action potential; SAP, sensory action potential.
*Use the picture below to discriminate the level of the symptoms.
†Uses aid *most of the time*. The patient was prescribed to wear/use or should be wearing/using the aid in the examiner's opinion (see written instructions, Table S2).
‡See written instructions for details of eligible foot surgery.
§Abnormal if patient says it is definitely decreased compared to a normal reference point.
‖Use Rydel-Seiffer tuning fork. Definition of normal: ≥5.
¶Limb strength scores refer to MRC grade.
**Intrinsic hand muscles strength assessment: test only abductor pollicis brevis (APB) and first dorsal interosseus (FDI), then choose the stronger to give the score.

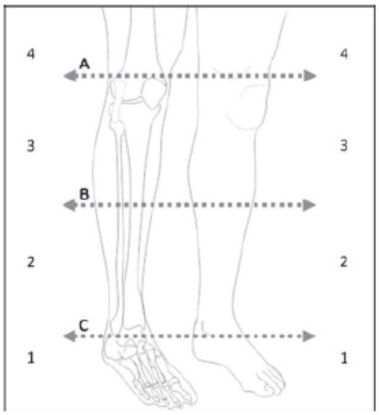

Table 2. CMTNS spoken instructions.

Sensory loss
Do you have loss of feeling anywhere in your feet or legs?
If so, does the loss of feeling extend above your toes?
Do they extend above the ankle?
Please identify the point on this drawing of the leg where the sensation becomes normal or nearly normal.
Are these symptoms constant (present all the time), present most of your daytime, less than one-half of the daytime, or just occasional? Daytime is defined as time between getting up and going to bed.
Motor symptoms (legs)
Do you have weakness in your legs or feet?
Do you ever trip over your toes/feet or turn or sprain your ankles?
Do your feet slap when you walk?
Do you wear shoe inserts/insoles (below the ankle)?
Do you wear braces, splints, or equivalent type of orthotics that extend above your ankle?
Have the above ankle orthotics described above ever been prescribed or suggested by healthcare professionals?
Have you had surgery on your feet or ankles?
If so, do you know if the surgery involved fusion of bones, a transfer of tendons, heel cord lengthening, or lowering of the arch?
Do you use a cane, stick, or walker to help you walk most of the time outside the home?
Do you use a wheelchair most of the time because of weakness?
Motor symptoms (arms)
Do you have difficulty with buttoning clothes (standard shirt buttons)?
If yes, are the difficulties mild or severe (severe includes unable)?
Can you cut most food including meat and pizza with normal utensils?
Do you have difficulty with activities that require extending or flexing your arms or activities using the upper arms?

iv. APPENDIX 4 - EQ-5D

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Under each heading, please tick the ONE box that best describes your health TODAY

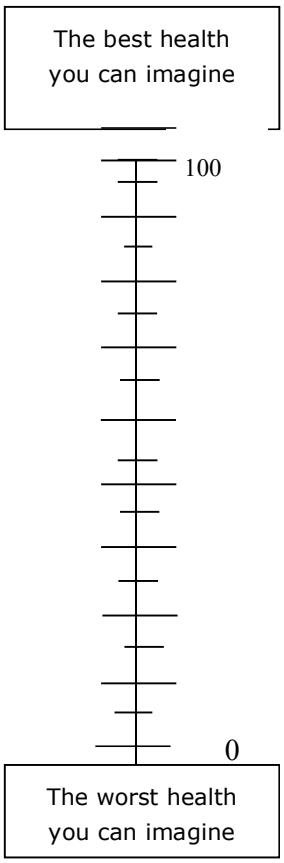
MOBILITY
I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

SELF-CARE
I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

PAIN / DISCOMFORT
I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

ANXIETY / DEPRESSION
I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed



In addition:

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100 (section of 1).
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

v. APPENDIX 5 - VAS ON SELF-ASSESSMENT OF THE INDIVIDUALIZED MAIN IMPAIRMENT IN DAILY ACTIVITIES DEFINED AT BASELINE WITH THE PATIENT

At baseline the patient will be asked by the investigator to select the main impairment (1 or 2) in his/her daily activities and to score it on a visual analogic scale. At each subsequent visit he will have to score it again.

1-Main impairment N° 1: describe……

How would you score your level of impairment today?

Place a vertical mark on the line below to indicate how impaired you feel today.

Not impaired Severely impaired

2-Main impairment N° 2: describe……

How would you score your level of impairment today?

Place a vertical mark on the line below to indicate how impaired you feel today.

Not impaired Severely impaired

Have you felt an improvement, regarding an impairment which you didn't mention during the previous visit(s)? Please describe what may have improved since the previous visit(s).

……
……
……