Clinical trial results:
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

Summary

EudraCT number	2015-002378-19
Trial protocol	FR DE ES BE GB NL
Global end of trial date	22 March 2018

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019
Summary attachment (see zip file)	CLN-PXT3003-02_Synopsis_CSR_190708 (CLN-PXT3003-02_Synopsis_CSR_190708.pdf)

Trial information

Trial identification

Sponsor protocol code	CLN-PXT3003-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02579759
WHO universal trial number (UTN)	-
Other trial identifiers	US IND: 122505

Notes:

Sponsors

Sponsor organisation name	PHARNEXT
Sponsor organisation address	Immeuble Vivaldi, 11-13 rue René Jacques, Issy Les Moulineaux, France, 92130
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002164-PIP01-17
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 March 2018
Global end of trial reached?	Yes
Global end of trial date	22 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of 2 doses of PXT3003 compared to Placebo on the disability measured by the Overall Neuropathy Limitation Scale (ONLS) score in CMT1A patients treated for 15 months.

Protection of trial subjects:

This study was conducted with the principles of the Declaration of Helsinki, the ICH and GCP guidelines, the study protocol, the European directives on clinical trials (Directive 2001/20/EC) and the applicable local country laws and regulations. Patients have been informed through the informed consent process of the possible or potential risks of each procedure. In case of children 16 to 18 year-old age, both parent's and children's consents were collected.

Background therapy:

PXT3003 was 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 were authorized during the entire study.

Evidence for comparator:

As there is no approved specific treatment in CMT1A, there is no active comparator to introduce; placebo was then used as control. PXT3003 or placebo were given on top of standard cares.

Actual start date of recruitment	11 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 63
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Spain: 62
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	France: 91
Country: Number of subjects enrolled	Germany: 67
Country: Number of subjects enrolled	Canada: 14
Worldwide total number of subjects	323
EEA total number of subjects	246

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	9
Adults (18-64 years)	314
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 100 subjects in each arm (Dose 2, Dose 1 and Placebo) were planned. Patients were randomized at a 1:1:1 ratio into the 3 parallel groups. First patients first visit occurred on 11-Dec-15 in FR, 21-Mar-16 in BE, 08-Apr-16 in DE, 01-Jun-16 in US, 28-Jun-16 in ES, 23-Aug-16 in NL, 29-Sep-16 in UK and 10-Nov-16 in CA

Pre-assignment

Screening details:

437 patients were screened for inclusion, between 11 December 2015 and 2 December 2016. Of those, 323 patients (73.9%) were randomized, 113 to the Dose 2 group, 109 to the Dose 1 group, and 101 to the Placebo group.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The treatment codes remained blinded until the time of the final statistical analysis following database lock. Dose 2 arm was unblinded at the time of the discontinuation on September 18th 2017 by sponsor decision.
Study treatments were numbered according to a material randomization list, separate from the subject randomization list.

Arms

Are arms mutually exclusive?	Yes
Arm title	PXT3003 Dose 2

Arm description:

Patients were randomized to the PXT3003 Dose 2 arm with a 1:1:1 ratio.

Arm type	Experimental
Investigational medicinal product name	PXT3003
Investigational medicinal product code	PXT3003 Dose 2
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

5mL administered twice daily, i.e. 10mL per day
PXT3003 Dose 2 corresponded to 6 mg baclofen, 0.70 mg naltrexone and 210 mg sorbitol given twice daily.

Arm title	PXT3003 Dose 1

Arm description:

Patients were randomized to the PXT3003 Dose 1 arm with a 1:1:1 ratio.

Arm type	Experimental
Investigational medicinal product name	PXT3003
Investigational medicinal product code	PXT3003 Dose 1
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

5mL administered twice daily, i.e. 10mL per day
PXT3003 Dose 1 corresponded to 3 mg baclofen, 0.35 mg naltrexone and 105 mg sorbitol given twice

daily.

Arm title	Placebo
Arm description: Patients were randomized to the Placebo arm with a 1:1:1 ratio.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details: 5mL administered twice daily, i.e. 10mL per day	

Number of subjects in period 1	PXT3003 Dose 2	PXT3003 Dose 1	Placebo
Started	113	109	101
Completed	49	85	80
Not completed	64	24	21
Inclusion/exclusion criteria	-	-	1
Consent withdrawn by subject	3	3	5
Adverse event, non-fatal	3	4	1
Other	1	-	-
Pregnancy	1	-	-
BfArM hold	12	13	12
Non-compliance	1	-	-
Sponsor stopped Dose 2	41	-	-
Lost to follow-up	2	2	2
Protocol deviation	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	PXT3003 Dose 2
Reporting group description:	
Patients were randomized to the PXT3003 Dose 2 arm with a 1:1:1 ratio.	
Reporting group title	PXT3003 Dose 1
Reporting group description:	
Patients were randomized to the PXT3003 Dose 1 arm with a 1:1:1 ratio.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized to the Placebo arm with a 1:1:1 ratio.	

Reporting group values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo
Number of subjects	113	109	101
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	4	4	1
Adults (18-64 years)	109	105	100
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	39.6	41.0	42.1
standard deviation	± 13.9	± 12.3	± 13.2
Gender categorical Units: Subjects			
Female	68	60	62
Male	45	49	39

Reporting group values	Total		
Number of subjects	323		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	9		
Adults (18-64 years)	314		

From 65-84 years	0		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	190		
Male	133		

End points

End points reporting groups

Reporting group title	PXT3003 Dose 2
Reporting group description:	
Patients were randomized to the PXT3003 Dose 2 arm with a 1:1:1 ratio.	
Reporting group title	PXT3003 Dose 1
Reporting group description:	
Patients were randomized to the PXT3003 Dose 1 arm with a 1:1:1 ratio.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized to the Placebo arm with a 1:1:1 ratio.	

Primary: Mean of the ONLS total score at Month 12 and Month 15

End point title	Mean of the ONLS total score at Month 12 and Month 15

End point description:

The primary efficacy variable is the mean of the ONLS score at month 12 and month 15 or the ONLS value at month 12 alone if no month 15 value was available.

The ONLS is a disability scale that was derived and improved from the Overall Disability Sum Score to measure limitations in the everyday activities of the upper limbs (rated on 5 points) and the lower limbs (rated on 7 points). The total score goes from 0 (no disability) to 12 (maximum disability). Lower values in the ONLS indicate a better clinical condition.

Reported values are the values at Baseline (Base) and the average of the available values at Month 12 and Month 15 (Fin).

End point type	Primary
End point timeframe:	
From Baseline to Month 15	

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55[1]	93[2]	87[3]	
Units: ONLS total score				
arithmetic mean (standard deviation)				
Base	3.05 (± 1.13)	3.33 (± 1.05)	3.23 (± 1.19)	
Fin	2.82 (± 1.28)	3.25 (± 1.00)	3.36 (± 1.16)	

Notes:

[1] - mFAS selection

[2] - mFAS selection

[3] - mFAS selection

Statistical analyses

Statistical analysis title	Main analysis for PXT3003 Dose 2

Statistical analysis description:

The main analysis was performed as follows:

1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	PXT3003 Dose 2 v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.68
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Main analysis for PXT3003 Dose 1

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.287
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.39
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	Longitudinal model (mFAS) - PXT3003 Dose 2

Statistical analysis description:

This analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)

2) Statistical model: Longitudinal model where the effect of each treatment over time (baseline, 6, 12 and 15 months) was estimated through a mixed model with repeated measures (MMRM) assuming time from baseline (Time) and Time-by-Treatment full interaction as fixed effects and patient as random effect and considering Time as continuous linear effect.
3) Missing value imputation: No imputation

Comparison groups	PXT3003 Dose 2 v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Longitudinal mixed model
Parameter estimate	Mean difference (final values)
Point estimate	-0.31
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.59
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Longitudinal model (mFAS) - PXT3003 Dose 1

Statistical analysis description:

This analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: Longitudinal model where the effect of each treatment over time (baseline, 6, 12 and 15 months) was estimated through a mixed model with repeated measures (MMRM) assuming time from baseline (Time) and Time-by-Treatment full interaction as fixed effects and patient as random effect and considering Time as continuous linear effect.
3) Missing value imputation: No imputation

Comparison groups	PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Longitudinal mixed model
Parameter estimate	Mean difference (net)
Point estimate	-0.19
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.42
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Relationship of Drug Dose to Response (mFAS)

Statistical analysis description:

Dose is defined as a numerical variable proportional to quantity of PXT3003 administered (0 for Placebo,

1 for Dose 1 and 2 for Dose 2).
The analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA assessing the dose-effect at the mean of 12 and 15 months, adjusting for baseline value and assuming centre as random effect
3) Missing value imputation: multiple imputation taking into account the reason of missingness

Comparison groups	PXT3003 Dose 2 v PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.07

Secondary: Mean change of the Ten Meter Walking Test (10MWT) score

End point title	Mean change of the Ten Meter Walking Test (10MWT) score

End point description:

The 10MWT is a simple to administer, standardized, reliable, and valid evaluation of functional exercise capacity and gait that has been used to evaluate neurologic disorders and CMT patients.

Lower Time to Walk 10 Meters values indicate a better clinical condition.

Reported values are the values at Baseline (Base) and the average of the available values at Month 12 and Month 15 (Fin)

End point type	Secondary

End point timeframe:

From Baseline to Month 15

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55[4]	93[5]	87[6]	
Units: Seconds (s)				
arithmetic mean (standard deviation)				
Base	7.14 (± 1.77)	6.93 (± 1.77)	7.28 (± 1.91)	
Fin	6.52 (± 1.39)	6.47 (± 1.59)	6.91 (± 1.82)	

Notes:

[4] - mFAS selection

[5] - mFAS selection

[6] - mFAS selection

Statistical analyses

Statistical analysis title	Main analysis for PXT3003 Dose 2

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	Placebo v PXT3003 Dose 2
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.91
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.19

Statistical analysis title	Main analysis for PXT3003 Dose 1

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	Placebo v PXT3003 Dose 1
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.084
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.28
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.65
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Relationship of Drug Dose to Response (mFAS)

Statistical analysis description:

Dose is defined as a numerical variable proportional to quantity of PXT3003 administered (0 for Placebo, 1 for Dose 1 and 2 for Dose 2).
And the analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA assessing the dose-effect at the mean of 12 and 15 months, adjusting for baseline value and assuming centre as random effect
3) Missing value imputation: multiple imputation taking into account the reason of missingness

Comparison groups	PXT3003 Dose 2 v PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Mean change of the CMTNS-v2 Sensory Score

End point title	Mean change of the CMTNS-v2 Sensory Score

End point description:

The CMTNS-v2 is a specific scale designed to assess severity of impairment in CMT disease. It is a 36-point scale based on nine items to quantify impairment (sensory symptoms, pin sensibility, vibration, and arm and leg strength), activity limitations (motor symptoms arms and legs), and electrophysiological function (amplitudes of ulnar CMAP and SNAP).
The CMTNS-v2 Sensory Score is calculated as the sum of items 1+4+5 of CMTNS-v2 (Sensory symptoms, Pinprick sensibility and Vibration).

Lower CMTNS-v2 Sensory Score values indicate a better clinical condition.

Reported values are the values at Baseline (Base) and the average of the available values at Month 12 and Month 15 (Fin)

End point type	Secondary

End point timeframe:

From Baseline to Month 15

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55[7]	93[8]	87[9]	
Units: CMTNS-2 score				
arithmetic mean (standard deviation)				
Base	4.47 (± 2.21)	5.00 (± 2.28)	4.97 (± 2.04)	
Fin	4.23 (± 2.38)	4.55 (± 1.96)	4.68 (± 2.14)	

Notes:

[7] - mFAS selection

[8] - mFAS selection

[9] - mFAS selection

Statistical analyses

Statistical analysis title	Main analysis for PXT3003 Dose 2

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	PXT3003 Dose 2 v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.39
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.01
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.28

Statistical analysis title	Main analysis for PXT3003 Dose 1

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.556
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.14

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.66
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	0.23

Statistical analysis title	Relationship of Drug Dose to Response (mFAS)

Statistical analysis description:

Dose is defined as a numerical variable proportional to quantity of PXT3003 administered (0 for Placebo, 1 for Dose 1 and 2 for Dose 2).
And the analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA assessing the dose-effect at the mean of 12 and 15 months, adjusting for baseline value and assuming centre as random effect
3) Missing value imputation: multiple imputation taking into account the reason of missingness

Comparison groups	PXT3003 Dose 2 v PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.204
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.13

Secondary: Mean change of the CMTNS-v2 Examination Score

End point title	Mean change of the CMTNS-v2 Examination Score

End point description:

The CMTNS-v2 is a specific scale designed to assess severity of impairment in CMT disease. It is a 36-point scale based on nine items to quantify impairment (sensory symptoms, pin sensibility, vibration, and arm and leg strength), activity limitations (motor symptoms arms and legs), and electrophysiological function (amplitudes of ulnar CMAP and SNAP).
The CMTNS-v2 Examination Score is limited to impairment items and excluding electrophysiological items (sum score of item 1 to 7).

Lower CMTNS-v2 Examination Score values indicate a better clinical condition.

Reported values are the values at Baseline (Base) and the average of the available values at Month 12 and Month 15 (Fin)

End point type	Secondary

End point timeframe:

From Baseline to Month 15

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55[10]	93[11]	87[12]	
Units: CMTNS score				
arithmetic mean (standard deviation)				
Base	8.78 (± 2.73)	9.49 (± 2.80)	9.51 (± 2.79)	
Fin	8.24 (± 3.13)	9.01 (± 2.62)	9.02 (± 3.05)	

Notes:

[10] - mFAS selection

[11] - mFAS selection

[12] - mFAS selection

Statistical analyses

Statistical analysis title	Main analysis for PXT3003 Dose 2

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	PXT3003 Dose 2 v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.25
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.36

Statistical analysis title	Main analysis for PXT3003 Dose 1

Statistical analysis description:

The main analysis was performed as follows:
(1) Analysis population: modified Full Analysis Set (mFAS)
(2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
(3) Imputation of missing values: multiple imputation taking into account reason of missingness

Comparison groups	Placebo v PXT3003 Dose 1

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.868
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.74
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.31

Statistical analysis title	Relationship of Drug Dose to Response (mFAS)

Statistical analysis description:

Dose is defined as a numerical variable proportional to quantity of PXT3003 administered (0 for Placebo, 1 for Dose 1 and 2 for Dose 2).
And the analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA assessing the dose-effect at the mean of 12 and 15 months, adjusting for baseline value and assuming centre as random effect
3) Missing value imputation: multiple imputation taking into account the reason of missingness

Comparison groups	PXT3003 Dose 1 v Placebo v PXT3003 Dose 2
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.322
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.18

Secondary: Mean change of the results at the Nine-Hole Peg Test

End point title	Mean change of the results at the Nine-Hole Peg Test

End point description:

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

Lower Nine-Hole Peg Test (9HPT) values indicate a better clinical condition.

Reported values are the values at Baseline (Base) and the average of the available values at Month 12

and Month 15 (Fin)

End point type	Secondary

End point timeframe:

From Baseline to Month 15

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55[13]	93[14]	87[15]	
Units: seconds (s)				
arithmetic mean (standard deviation)				
Base	27.33 (± 11.15)	25.62 (± 5.60)	25.18 (± 4.41)	
Fin	25.67 (± 8.29)	23.85 (± 4.52)	24.41 (± 4.01)	

Notes:

[13] - mFAS selection

[14] - mFAS selection

[15] - mFAS selection

Statistical analyses

Statistical analysis title	Main analysis for PXT3003 Dose 2

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	PXT3003 Dose 2 v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.377
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.43
upper limit	0.62
Variability estimate	Standard error of the mean
Dispersion value	0.46

Statistical analysis title	Main analysis for PXT3003 Dose 1

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)

2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	Placebo v PXT3003 Dose 1
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.334
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.21
upper limit	0.48
Variability estimate	Standard error of the mean
Dispersion value	0.38

Statistical analysis title	Relationship of Drug Dose to Response (mFAS)

Statistical analysis description:

Dose is defined as a numerical variable proportional to quantity of PXT3003 administered (0 for Placebo, 1 for Dose 1 and 2 for Dose 2).
And the analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA assessing the dose-effect at the mean of 12 and 15 months, adjusting for baseline value and assuming centre as random effect
3) Missing value imputation: multiple imputation taking into account the reason of missingness

Comparison groups	PXT3003 Dose 2 v PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.373
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.22

Secondary: Incidence of all TEAEs

End point title	Incidence of all TEAEs

End point description:

Safety selection was to include all randomized patients that have received at least one dose of study

treatment.

Safety and tolerability of PXT3003 were compared to placebo on the incidence of treatment-emergent adverse events (TEAEs); they were evaluated by type/nature, severity/intensity, seriousness, and relationship to study drug.

End point type	Secondary

End point timeframe:

The period between the patient signing the informed consent and 30 days after the end of study (i.e. completion/early discontinuation/last contact as recorded on the 'Study Completion on Early Termination' form)

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	109	101	
Units: number of TEAEs				
number (not applicable)				
Any TEAE	87	89	83	
Any related TEAE	38	39	34	
Any moderately severe or severe related TEAE	5	8	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of AE leading to withdrawal of study drug

End point title	Incidence of AE leading to withdrawal of study drug

End point description:

Safety and tolerability of PXT3003 were compared to placebo on the incidence of TEAEs leading to withdrawal of study drug.

End point type	Secondary

End point timeframe:

The period between the patient signing the informed consent and 30 days after the end of study (i.e. completion/early discontinuation/last contact as recorded on the 'Study Completion on Early Termination' form).

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	109	101	
Units: number of TEAEs				
number (not applicable)				
Any TEAE leading to drug withdrawal	6	6	6	
Any related TEAE leading to drug withdrawal	2	3	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of SAEs

End point title	Incidence of SAEs

End point description:

Safety and tolerability of PXT3003 were compared to placebo on the incidence of serious adverse events (SAEs).

End point type	Secondary

End point timeframe:

The period between the patient signing the informed consent and 30 days after the end of study (i.e. completion/early discontinuation/last contact as recorded on the 'Study Completion on Early Termination' form).

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	109	101	
Units: number of TEAE				
number (not applicable)				
Any serious TEAE	3	10	5	
Any related serious TEAE	0	0	0	
Any serious TEAE leading to drug withdrawal	0	1	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma concentrations of baclofen at trough and at peak

End point title	Plasma concentrations of baclofen at trough and at peak[16]

End point description:

Plasma concentration of PXT3003 components were measured at trough (prior to dose) and peak (90 minutes post dose).
The mean plasma values of the base correspond to half of the administered dose.

End point type	Other pre-specified

End point timeframe:

At 12 months, and 15 months.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For Placebo the values correspond to LLOQ: 30 pg/mL

End point values	PXT3003 Dose 2	PXT3003 Dose 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[17]	68[18]		
Units: pg/mL				
arithmetic mean (standard deviation)				
At trough, at Month 12	11651.9 (± 6151.1)	13739.3 (± 20313.6)		
At trough, at Month 15	8686.6 (± 9172.8)	9009.7 (± 10910.3)		
At peak, at Month 12	90238.7 (± 29972.8)	52201.6 (± 21494.6)		
At peak, at Month 15	105825.4 (± 38756.7)	47021.1 (± 19834.5)		

Notes:

[17] - PP selection
LLOQ = 30 pg/mL
[18] - PP selection
LLOQ = 30 pg/mL

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma concentrations of naltrexone at trough and at peak

End point title	Plasma concentrations of naltrexone at trough and at peak[19]

End point description:

Plasma concentration of PXT3003 components were measured at trough (prior to dose) and peak (90 minutes post dose).
The mean plasma values of the base correspond to half of the administered dose.

End point type	Other pre-specified

End point timeframe:

At Month 12 and at Month 15

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For Placebo the values correspond to LLOQ: 30 pg/mL

End point values	PXT3003 Dose 2	PXT3003 Dose 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[20]	68[21]		
Units: pg/mL				
arithmetic mean (standard deviation)				
At trough, at Month 12	42.0 (± 66.0)	33.0 (± 15.8)		
At trough, at Month 15	30.0 (± 0.0)	31.8 (± 14.0)		
At peak, at Month 12	107.5 (± 88.6)	63.0 (± 47.4)		
At peak, at Month 15	130.9 (± 81.4)	55.0 (± 39.3)		

Notes:

[20] - PP selection
LLOQ = 30 pg/mL
[21] - PP selection
LLOQ = 30 pg/mL

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma concentrations of 6β-naltrexol at trough and at peak

End point title	Plasma concentrations of 6β-naltrexol at trough and at peak[22]

End point description:

Plasma concentration of PXT3003 components were measured at trough (prior to dose) and peak (90 minutes post dose).
The mean plasma values of the base correspond to half of the administered dose.

End point type	Other pre-specified

End point timeframe:

At Month 12 and at Month 15

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For Placebo the values correspond to LLOQ: 50 pg/mL

End point values	PXT3003 Dose 2	PXT3003 Dose 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[23]	68[24]		
Units: pg/mL				
arithmetic mean (standard deviation)				
At trough, at Month 12	526.4 (± 245.6)	290.1 (± 177.4)		
At trough, at Month 15	352.3 (± 319.0)	260.4 (± 121.8)		
At peak, at Month 12	1257.1 (± 454.3)	632.5 (± 230.1)		
At peak, at Month 15	1450.9 (± 438.0)	586.4 (± 205.4)		

Notes:

[23] - PP selection
LLOQ = 50 pg/mL
[24] - PP selection
LLOQ = 50 pg/mL

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change CMTNS-v2 Sensory Symptoms

End point title	Mean change CMTNS-v2 Sensory Symptoms

End point description:

The CMTNS-v2 is a specific scale designed to assess severity of impairment in CMT disease. It is a 36-point scale based on nine items to quantify impairment (sensory symptoms, pin sensibility, vibration, and arm and leg strength), activity limitations (motor symptoms arms and legs), and electrophysiological function (amplitudes of ulnar CMAP and SNAP).

The CMTNS-v2 Sensory symptoms is the first item of the CMTNS-v2.

Lower values in the CMTNS-v2 Sensory Symptoms indicate a better clinical condition.

Reported values are the values at Baseline (Base) and the average of the available values at Month 12 and Month 15 (Fin)

End point type	Other pre-specified

End point timeframe:

From Baseline to Month 15

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55[25]	93[26]	87[27]	
Units: CMTNS score				
arithmetic mean (standard deviation)				
Base	0.96 (± 0.98)	1.26 (± 0.95)	1.09 (± 0.90)	
Fin	0.93 (± 0.96)	1.18 (± 0.81)	1.21 (± 0.94)	

Notes:

[25] - mFAS selection

[26] - mFAS selection

[27] - mFAS selection

Statistical analyses

Statistical analysis title	Main analysis for PXT3003 Dose 2

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	PXT3003 Dose 2 v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.29
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.58
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Main analysis for PXT3003 Dose 1

Statistical analysis description:

The main analysis was performed as follows:
1) Analysis population: modified Full Analysis Set (mFAS)
2) Statistical model: ANCOVA where the mean at 12 and 15 months of each treatment group was compared against the placebo group, adjusting for the baseline value and assuming centre as a random effect
3) Missing value imputation: multiple imputation taking into account reason of missingness

Comparison groups	PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.4
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.11

Other pre-specified: ONLS Therapy Response 1

End point title	ONLS Therapy Response 1

End point description:

ONLS Therapy Response 1 was defined as improvement on final ONLS Total Score of at least one point. A higher response rate indicates a better clinical condition.

Reported values are the average of the available values at Month 12 and Month 15 (Fin).

End point type	Other pre-specified

End point timeframe:

From Baseline to Month 15

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49[28]	85[29]	80[30]	
Units: Responders				
number (not applicable)	14	16	14	

Notes:

[28] - Completers selection

[29] - Completers selection

[30] - Completers selection

Statistical analyses

Statistical analysis title	Responder Analysis - PXT3003 Dose 2 (Completers)

Statistical analysis description:

The proportion of responders (on Completers selection only) at the end of treatment was assessed through a Generalized Linear Mixed Model (GLMM) featuring logistic regression including treatment as a fixed effect, adjusting for the baseline value and center as a random effect.

Comparison groups	PXT3003 Dose 2 v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097
Method	General Linear Mixed Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.09
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.77
upper limit	5.68

Statistical analysis title	Responder Analysis - PXT3003 Dose 1 (Completers)

Statistical analysis description:

The proportion of responders (on Completers selection only) at the end of treatment was assessed through a Generalized Linear Mixed Model (GLMM) featuring logistic regression including treatment as a fixed effect, adjusting for the baseline value and center as a random effect.

Comparison groups	Placebo v PXT3003 Dose 1
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.865
Method	General Linear Mixed Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.42
upper limit	2.7

Other pre-specified: ONLS Therapy Response 2

End point title	ONLS Therapy Response 2

End point description:

ONLS Therapy Response 2 was defined as no deterioration on final ONLS Total Score. A higher response rate indicates a better clinical condition.

Reported values are the average of the available values at Month 12 and Month 15 (Fin).

End point type	Other pre-specified

End point timeframe:

From Baseline to Month 15

End point values	PXT3003 Dose 2	PXT3003 Dose 1	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49[31]	85[32]	80[33]	
Units: Responders				
number (not applicable)	42	66	58	

Notes:

[31] - Completers selection

[32] - Completers selection

[33] - Completers selection

Statistical analyses

Statistical analysis title	Responder Analysis - PXT3003 Dose 2 (Completers)

Statistical analysis description:

The proportion of responders (on Completers selection only) at the end of treatment was assessed through a Generalized Linear Mixed Model (GLMM) featuring logistic regression including treatment as a fixed effect and center as a random effect.

Comparison groups	PXT3003 Dose 2 v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	General Linear Mixed Model
Parameter estimate	Odds ratio (OR)
Point estimate	3.39
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.99
upper limit	11.62

Statistical analysis title	Responder Analysis - PXT3003 Dose 1 (Completers)

Statistical analysis description:

The proportion of responders (on Completers selection only) at the end of treatment was assessed through a Generalized Linear Mixed Model (GLMM) featuring logistic regression including treatment as a fixed effect and center as a random effect.

Comparison groups	PXT3003 Dose 1 v Placebo
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.569
Method	General Linear Mixed Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.26

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.5
upper limit	3.16

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period therefore started with the subject signing the informed consent form and ended 30 days after the end of study (corresponding to the date of "Date of completion/early discontinuation/last contact" recorded in the termination module)

Adverse event reporting additional description:

This definition was extended due to the discontinuation of Dose 2 and study on hold in Germany. The period of AE reporting was extended to 1 month after the end of study, without informed consent signed for study CLN-PXT3003-03 during this period.
Only Treatment-Emergent Adverse Events (TEAE) have been reported for non-serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	PXT3003 Dose 2

Reporting group description:

The subjects have been randomized to the PXT3003 Dose 2 arm with a 1:1:1 ratio.
PXT3003 Dose 2 corresponds to 6 mg baclofen, 0.70 mg naltrexone and 210 mg sorbitol given twice daily.

Reporting group title	PXT3003 Dose 1

Reporting group description:

The subjects have been randomized to the PXT3003 Dose 1 arm with a 1:1:1 ratio.
PXT3003 Dose 1 corresponds to 3 mg baclofen, 0.35 mg naltrexone and 105 mg sorbitol given twice daily.

Reporting group title	Placebo

Reporting group description:

The subjects have been randomized to the Placebo arm with a 1:1:1 ratio.

Serious adverse events	PXT3003 Dose 2	PXT3003 Dose 1	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 113 (2.65%)	10 / 109 (9.17%)	5 / 101 (4.95%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid adenoma			

subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Arthrolysis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			

subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Median nerve injury			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital foot malformation			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patent ductus arteriosus			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Proctitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Chest wall haematoma			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	PXT3003 Dose 2	PXT3003 Dose 1	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 113 (76.99%)	89 / 109 (81.65%)	83 / 101 (82.18%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 113 (0.88%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	1	1	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 113 (1.77%)	3 / 109 (2.75%)	7 / 101 (6.93%)
occurrences (all)	2	3	9
Fatigue			
subjects affected / exposed	2 / 113 (1.77%)	11 / 109 (10.09%)	6 / 101 (5.94%)
occurrences (all)	2	15	6
Influenza like illness			
subjects affected / exposed	6 / 113 (5.31%)	3 / 109 (2.75%)	0 / 101 (0.00%)
occurrences (all)	9	5	0
Peripheral swelling			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	2 / 101 (1.98%)
occurrences (all)	0	0	2
Oropharyngeal pain			

subjects affected / exposed	2 / 113 (1.77%)	3 / 109 (2.75%)	5 / 101 (4.95%)
occurrences (all)	2	6	8
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 113 (1.77%)	3 / 109 (2.75%)	2 / 101 (1.98%)
occurrences (all)	3	3	2
Depression			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	5 / 101 (4.95%)
occurrences (all)	0	1	5
Insomnia			
subjects affected / exposed	1 / 113 (0.88%)	1 / 109 (0.92%)	3 / 101 (2.97%)
occurrences (all)	1	4	3
Sleep disorder			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	2	1	2
Investigations			
Weight increased			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	5 / 101 (4.95%)
occurrences (all)	0	1	6
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 113 (0.88%)	1 / 109 (0.92%)	3 / 101 (2.97%)
occurrences (all)	1	1	4
Fall			
subjects affected / exposed	3 / 113 (2.65%)	9 / 109 (8.26%)	7 / 101 (6.93%)
occurrences (all)	3	15	9
Laceration			
subjects affected / exposed	0 / 113 (0.00%)	3 / 109 (2.75%)	0 / 101 (0.00%)
occurrences (all)	0	3	0
Ligament sprain			
subjects affected / exposed	2 / 113 (1.77%)	8 / 109 (7.34%)	9 / 101 (8.91%)
occurrences (all)	2	9	12
Limb injury			
subjects affected / exposed	1 / 113 (0.88%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	1	1	2
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	2 / 101 (1.98%)
occurrences (all)	1	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 113 (4.42%)	9 / 109 (8.26%)	2 / 101 (1.98%)
occurrences (all)	5	10	3
Headache			
subjects affected / exposed	13 / 113 (11.50%)	17 / 109 (15.60%)	11 / 101 (10.89%)
occurrences (all)	20	22	14
Hypoaesthesia			
subjects affected / exposed	3 / 113 (2.65%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	3	1	2
Migraine			
subjects affected / exposed	3 / 113 (2.65%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	3	2	3
Paraesthesia			
subjects affected / exposed	3 / 113 (2.65%)	2 / 109 (1.83%)	0 / 101 (0.00%)
occurrences (all)	5	2	0
Sciatica			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	2	1	3
Somnolence			
subjects affected / exposed	2 / 113 (1.77%)	5 / 109 (4.59%)	1 / 101 (0.99%)
occurrences (all)	2	5	1
Tremor			
subjects affected / exposed	3 / 113 (2.65%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences (all)	3	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 113 (0.88%)	2 / 109 (1.83%)	2 / 101 (1.98%)
occurrences (all)	1	2	2
Vertigo			
subjects affected / exposed	1 / 113 (0.88%)	3 / 109 (2.75%)	2 / 101 (1.98%)
occurrences (all)	1	4	2
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	5 / 113 (4.42%)	2 / 109 (1.83%)	3 / 101 (2.97%)
occurrences (all)	5	2	4
Abdominal pain upper			
subjects affected / exposed	4 / 113 (3.54%)	3 / 109 (2.75%)	3 / 101 (2.97%)
occurrences (all)	5	3	3
Constipation			
subjects affected / exposed	2 / 113 (1.77%)	4 / 109 (3.67%)	2 / 101 (1.98%)
occurrences (all)	2	4	2
Diarrhoea			
subjects affected / exposed	7 / 113 (6.19%)	7 / 109 (6.42%)	7 / 101 (6.93%)
occurrences (all)	8	9	8
Dry mouth			
subjects affected / exposed	3 / 113 (2.65%)	3 / 109 (2.75%)	4 / 101 (3.96%)
occurrences (all)	3	3	4
Dyspepsia			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	3 / 101 (2.97%)
occurrences (all)	2	1	4
Nausea			
subjects affected / exposed	7 / 113 (6.19%)	12 / 109 (11.01%)	6 / 101 (5.94%)
occurrences (all)	7	17	6
Toothache			
subjects affected / exposed	0 / 113 (0.00%)	4 / 109 (3.67%)	1 / 101 (0.99%)
occurrences (all)	0	4	1
Vomiting			
subjects affected / exposed	5 / 113 (4.42%)	2 / 109 (1.83%)	1 / 101 (0.99%)
occurrences (all)	5	2	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 113 (1.77%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	2	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 113 (2.65%)	13 / 109 (11.93%)	8 / 101 (7.92%)
occurrences (all)	3	19	8
Back pain			

subjects affected / exposed	5 / 113 (4.42%)	10 / 109 (9.17%)	3 / 101 (2.97%)
occurrences (all)	5	12	3
Bone callus excessive			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	2 / 101 (1.98%)
occurrences (all)	0	0	2
Joint swelling			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	4 / 101 (3.96%)
occurrences (all)	0	1	4
Muscle spasms			
subjects affected / exposed	8 / 113 (7.08%)	5 / 109 (4.59%)	6 / 101 (5.94%)
occurrences (all)	9	7	6
Musculoskeletal pain			
subjects affected / exposed	4 / 113 (3.54%)	1 / 109 (0.92%)	1 / 101 (0.99%)
occurrences (all)	4	1	1
Myalgia			
subjects affected / exposed	1 / 113 (0.88%)	3 / 109 (2.75%)	2 / 101 (1.98%)
occurrences (all)	1	3	2
Neck pain			
subjects affected / exposed	3 / 113 (2.65%)	3 / 109 (2.75%)	3 / 101 (2.97%)
occurrences (all)	3	4	3
Osteoarthritis			
subjects affected / exposed	2 / 113 (1.77%)	3 / 109 (2.75%)	0 / 101 (0.00%)
occurrences (all)	2	3	0
Pain in extremity			
subjects affected / exposed	5 / 113 (4.42%)	10 / 109 (9.17%)	9 / 101 (8.91%)
occurrences (all)	6	13	13
Rotator cuff syndrome			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	3 / 101 (2.97%)
occurrences (all)	0	0	4
Tendonitis			
subjects affected / exposed	3 / 113 (2.65%)	2 / 109 (1.83%)	4 / 101 (3.96%)
occurrences (all)	3	2	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 113 (0.88%)	2 / 109 (1.83%)	6 / 101 (5.94%)
occurrences (all)	1	3	6

Cystitis			
subjects affected / exposed	0 / 113 (0.00%)	2 / 109 (1.83%)	2 / 101 (1.98%)
occurrences (all)	0	3	2
Gastroenteritis			
subjects affected / exposed	3 / 113 (2.65%)	3 / 109 (2.75%)	5 / 101 (4.95%)
occurrences (all)	3	4	5
Influenza			
subjects affected / exposed	6 / 113 (5.31%)	3 / 109 (2.75%)	3 / 101 (2.97%)
occurrences (all)	6	3	3
Nasopharyngitis			
subjects affected / exposed	18 / 113 (15.93%)	24 / 109 (22.02%)	15 / 101 (14.85%)
occurrences (all)	26	31	24
Pharyngitis			
subjects affected / exposed	0 / 113 (0.00%)	2 / 109 (1.83%)	2 / 101 (1.98%)
occurrences (all)	0	2	2
Respiratory tract infection			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	0	1	2
Rhinitis			
subjects affected / exposed	3 / 113 (2.65%)	3 / 109 (2.75%)	4 / 101 (3.96%)
occurrences (all)	4	3	5
Sinusitis			
subjects affected / exposed	6 / 113 (5.31%)	7 / 109 (6.42%)	1 / 101 (0.99%)
occurrences (all)	6	8	1
Tracheitis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 109 (0.00%)	2 / 101 (1.98%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 113 (0.88%)	2 / 109 (1.83%)	2 / 101 (1.98%)
occurrences (all)	1	2	2
Urinary tract infection			
subjects affected / exposed	3 / 113 (2.65%)	1 / 109 (0.92%)	2 / 101 (1.98%)
occurrences (all)	5	1	2
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	3 / 113 (2.65%)	0 / 109 (0.00%)	1 / 101 (0.99%)
occurrences (all)	3	0	1
Vitamin D deficiency			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	3 / 101 (2.97%)
occurrences (all)	1	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2015	The study protocol was updated from version 1.0 dated 22 May 2015 to version 1.1 dated 01 September 2015 to add an interim analysis and minor changes in the presentation of the protocol to harmonize all protocols for all countries.
19 January 2016	The study protocol was updated from version 1.1 dated 01 September 2015 to version 1.2 dated 19 January 2016, the main change was the following: Calf MRI changes in leg MRI and added possibility to perform the PMP22 duplication genetic test if not already documented in patient history (only for US).
14 October 2016	The study protocol was updated from version 1.2 dated 19 January 2016 to version 1.3 dated 14 October 2016, the main changes were the following: Removing of SynteractHCR CRO name on the cover page, correction Typo error in section 13.1, 2nd§: written 6β-naltrexol instead of 6β-naltrexone.
18 January 2017	The study protocol was updated from version 1.3 dated 14 October 2016 to version 1.4 dated 18 January 2017, the main changes were the following: 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.
05 December 2017	The study protocol was updated from version 1.4 dated 18 January 2017 to version 1.5 dated 05 December 2017, the main changes were the followings: 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 CLNPXT3003-03 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

27 June 2017	In March 2017, during the course of the clinical study, crystals were reported by patients in some vials of the Dose 2 Investigational Medicinal Product. Based on that , the study was put on hold in Germany by BfArM in July 2017. The crystals were subsequently confirmed in an 18-month stability testing of the Dose 2 formulation of PXT3003 on September 14, 2017. Despite the lack of safety concerns reported by the data safety monitoring board on September 5, 2017, the Sponsor's decision was to discontinue the Dose 2 arm patients still under treatment on September 18, 2017. The remaining patients on Dose 1 and Placebo continued the study in a blinded fashion. Patients of the PXT3003 dose 2 arm terminated the study early and were offered to enter the extension study CLN-PXT3003-03. They received the equivalent of dose 2 (5 mL per administration), by using twice the dose 1 IMP (2x5 mL, i.e. 10 mL) per administration.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Two events occured during the trial due to crystals: hold of all subjects enrolled in Germany (Jun-17) and discontinuation of Dose 2 arm by the sponsor worldwide due to the discovery of crystals in the ICH stability batch in Sep-17.

Notes: