

**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 |
| Public contact | Susanne Dorn, PHARNEXT, +33 (0)1 41 09 22 30, contact@pharnext.com |
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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) | EMA-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 6 β -naltrexol at trough and at peak

| | |
|-----------------|---|
| End point title | Plasma concentrations of 6 β -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 (\pm 245.6) | 290.1 (\pm 177.4) | | |
| At trough, at Month 15 | 352.3 (\pm 319.0) | 260.4 (\pm 121.8) | | |
| At peak, at Month 12 | 1257.1 (\pm 454.3) | 632.5 (\pm 230.1) | | |
| At peak, at Month 15 | 1450.9 (\pm 438.0) | 586.4 (\pm 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 occurrences (all) | 2 / 113 (1.77%) 2 | 3 / 109 (2.75%) 6 | 5 / 101 (4.95%) 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 occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 109 (0.00%) 0 | 2 / 101 (1.98%) 3 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 5 / 113 (4.42%) 5 | 9 / 109 (8.26%) 10 | 2 / 101 (1.98%) 3 |
| Headache subjects affected / exposed occurrences (all) | 13 / 113 (11.50%) 20 | 17 / 109 (15.60%) 22 | 11 / 101 (10.89%) 14 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 3 / 113 (2.65%) 3 | 1 / 109 (0.92%) 1 | 2 / 101 (1.98%) 2 |
| Migraine subjects affected / exposed occurrences (all) | 3 / 113 (2.65%) 3 | 1 / 109 (0.92%) 2 | 2 / 101 (1.98%) 3 |
| Paraesthesia subjects affected / exposed occurrences (all) | 3 / 113 (2.65%) 5 | 2 / 109 (1.83%) 2 | 0 / 101 (0.00%) 0 |
| Sciatica subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 2 | 1 / 109 (0.92%) 1 | 2 / 101 (1.98%) 3 |
| Somnolence subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 2 | 5 / 109 (4.59%) 5 | 1 / 101 (0.99%) 1 |
| Tremor subjects affected / exposed occurrences (all) | 3 / 113 (2.65%) 3 | 0 / 109 (0.00%) 0 | 1 / 101 (0.99%) 1 |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 2 / 109 (1.83%) 2 | 2 / 101 (1.98%) 2 |
| Vertigo subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 3 / 109 (2.75%) 4 | 2 / 101 (1.98%) 2 |
| Gastrointestinal disorders | | | |

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|--------------|---|---|
| 27 June 2017 | <p>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.</p> <p>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.</p> | - |
|--------------|---|---|

Notes:

Limitations and caveats

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

Two events occurred 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: