

**Clinical trial results:**

A randomised, double-blind, double-dummy, parallel-group multicenter study to demonstrate improvement in symptoms of constipation and non-inferiority in analgesic efficacy in subjects with non-malignant or malignant pain that requires around-the-clock opioid therapy taking 50/25-80/40 mg twice daily as oxycodone/naloxone prolonged release (OXN PR) tablets compared to subjects taking 50-80 mg twice daily oxycodone prolonged release (OxyPR) tablets alone. During the open-label Extension Phase the efficacy and safety of OXN PR were assessed in doses up to OXN90/45 mg PR twice daily.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2010-021995-27 |
| Trial protocol | GB CZ DE FI DK RO |
| Global end of trial date | 18 August 2014 |

Results information

| | |
|--------------------------------|---|
| Result version number | v3 (current) |
| This version publication date | 08 July 2016 |
| First version publication date | 12 August 2015 |
| Version creation reason | <ul style="list-style-type: none">Changes to summary attachmentsRemove user due to them leaving the company. |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | OXN3506 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01438567 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Mundipharma Research GmbH & Co. KG |
| Sponsor organisation address | Höhenstrasse 10, Limburg, Germany, D-65549 |
| Public contact | Clinical Trial Contact, Mundipharma Research GmbH & Co. KG, 0044 1223424900, info@contact-clinical-trial.com |
| Scientific contact | Clinical Trial Contact, Mundipharma Research GmbH & Co. KG, 0044 1223424900, info@contact-clinical-trial.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| 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? | No |
|--|----|

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 18 August 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 August 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 August 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Core study phase:

1. To demonstrate that subjects taking OXN PR have improvement in symptoms of constipation as measured by the Bowel Function Index (BFI) compared to subjects taking OxyPR.
2. To demonstrate non-inferiority of OXN PR compared to OxyPR with respect to the analgesic efficacy based on the subjects' "Average Pain over last 24 Hours" assessed at each Double-blind Phase visit as measured by the Pain Intensity Scale.

Extension Phase:

3. To assess bowel function, pain and safety parameters.

Protection of trial subjects:

The approved dose range of OXN PR is up to OXN80/40 mg PR per day, which is sufficient to manage a significant segment of the population of patients with severe pain. However, it is evident that there is a need of OXN PR daily doses higher than 80/40 mg. Currently, in the OXN PR SmPC allowance for this situation is made by the compromise that "for patients requiring higher doses of OXN PR, administration of supplemental oxycodone at the same time interval should be considered taking into account the maximum daily dose of 400 mg oxycodone PR". However it is to be considered that in the case of supplemental oxycodone dosing the beneficial effect of naloxone on the bowel function may be impaired as also outlined in the current SmPC. Consequently, patients in need of higher doses would clearly benefit from the maintenance of the 2:1 ratio in doses beyond OXN80/40 mg PR per day. Based on the results from the Double-blind Phase of this study, it can be assumed that OXN PR can be used safely in patients requiring daily doses up to OXN160/80 mg PR per day. It is not expected that long-term use will cause any additional safety issues.

Based on the available data, there is accumulating evidence that OXN PR is efficacious and generally well tolerated in doses up to OXN160/80 mg PR per day.

Therefore it can be assumed that OXN PR can be used safely in patients requiring daily doses above OXN 80/40 mg PR per day and the administration of daily dose up to OXN180/90 mg PR in study OXN3506 does not add any risk to the subjects.

OxyIR was the only allowed analgesic rescue medication. It was to be dosed no sooner than every 4 hours as needed. Six rescue doses of OxyIR was the total maximum amount of analgesic rescue medication per day. For a subject stabilised on 50 mg of OXN PR or OxyPR twice daily, the rescue dose of OxyIR would have been 15 mg; for a subject stabilised on 60 mg of OXN PR or OxyPR twice daily, the rescue dose of OxyIR would have been 20 mg; for a subject stab

Background therapy:

Oxycodone immediate-release (IR) capsules (5, 10, 20 mg) was the only allowed analgesic rescue medication. It was to be dosed no sooner than every 4 hours as needed. Six rescue doses of OxyIR was the total maximum amount of analgesic rescue medication per day. For a subject stabilised on 50 mg of OXN PR or OxyPR twice daily, the rescue dose of OxyIR would have been 15 mg; for a subject stabilised on 60 mg of OXN PR or OxyPR twice daily, the rescue dose of OxyIR would have been 20 mg; for a subject stabilised on 70 or 80 mg of OXN PR or OxyPR twice daily, the rescue dose of OxyIR would have been 25 mg.

Oral bisacodyl could be used as laxative rescue medication for constipation, no sooner than 72 hours after the subject's most recent bowel movement. However, Investigators instructed their subjects that if they exhibited discomfort during the 72 hours period they could take oral bisacodyl as a laxative rescue

medication for the treatment of constipation earlier than 72 hours after their most recent bowel movement. Overall the maximum allowed amount of bisacodyl was not to exceed 5 dosages bisacodyl 10 mg/day within 7 consecutive days. At the discretion of the Investigator, the bisacodyl dose may have been lowered (5 mg) if the Investigator/subject felt that the dose was higher than required to provide an adequate bowel movement.

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 15 August 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 4 |
| Country: Number of subjects enrolled | Israel: 1 |
| Country: Number of subjects enrolled | Poland: 55 |
| Country: Number of subjects enrolled | Romania: 8 |
| Country: Number of subjects enrolled | United Kingdom: 27 |
| Country: Number of subjects enrolled | Czech Republic: 62 |
| Country: Number of subjects enrolled | Denmark: 12 |
| Country: Number of subjects enrolled | Finland: 3 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 69 |
| Worldwide total number of subjects | 243 |
| EEA total number of subjects | 238 |

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) | 0 |
| Adults (18-64 years) | 181 |
| From 65 to 84 years | 61 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

All 243 subjects were enrolled at 66 sites in 11 countries between 26 Sep 2011 and 21 Nov 2013.

Pre-assignment

Screening details:

363 subjects were enrolled, of whom 44 (12.1%) subjects were screening failures. The most frequently named reason for screening failure was failing of screening procedures in 25 subjects (6.9%). Adverse events led to the screening failure of 8 subjects (2.2%) and serious adverse events caused 3 screening failures (0.8%).

Period 1

| | |
|------------------------------|---|
| Period 1 title | Core study |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

During the double-blind Phase, the subject and all personnel involved with the conduct and the interpretation of the study, including the investigators, site personnel, and the Sponsor's staff, were blinded to the medication codes. The randomisation schedule was filed securely by the Sponsor/IRT provider, in a manner such that blinding was properly maintained throughout the study.

Arms

| | |
|--|--------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | OXN PR |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Oxycodone/naloxone prolonged release |
| Investigational medicinal product code | OXN PR |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10/5, 20/10, and 40/20 mg OXN PR tablets administered 12 -hourly to give the following dose levels: OXN 50/25 mg PR, OXN 60/30 mg PR, OXN 70/35 mg PR and OXN 80/40 mg PR twice daily

| | |
|--|-----------------------------|
| Arm title | OxyPR |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Oxycodone prolonged release |
| Investigational medicinal product code | OxyPR |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10, 20, and 40 mg OxyPR tablets plus matching placebos for 10/5, 20/10 and 40/20 mg OXN PR tablets to give dose levels of: OxyPR 50 mg, OxyPR 60 mg, OxyPR 70 mg and OxyPR 80 mg twice daily.

| Number of subjects in period 1 | OXN PR | OxyPR |
|--------------------------------|--------|-------|
| Started | 123 | 120 |
| Completed | 105 | 104 |
| Not completed | 18 | 16 |
| Adverse event, serious fatal | 1 | 3 |
| Consent withdrawn by subject | 6 | 8 |
| Administrative | - | 2 |
| Adverse event, non-fatal | 8 | 2 |
| Not specified | 1 | - |
| Lack of efficacy | 2 | 1 |

Period 2

| | |
|------------------------------|----------------|
| Period 2 title | Extension |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|--------------------|
| Arm title | OXN PR (Extension) |
|-----------|--------------------|

Arm description:

Subjects who completed the 5 weeks Double-blind Phase, or subjects who discontinued the Double-blind Phase prematurely due to constipation, were eligible to enter the Extension Phase, which consisted of additional 24 weeks treatment with open-label OXN PR up to a maximum dose of OXN90/45 mg PR twice daily.

| | |
|--|--------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Oxycodone/naloxone prolonged release |
| Investigational medicinal product code | OXN PR |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

All subjects who entered the Extension Phase started with the OxyPR dose which the subjects received at the end of the double-blind phase/early discontinuation. The switch to open-label OXN PR was done in a stepwise, double-blind, double-dummy manner during the first week of the Extension Phase. OxyIR was provided for the first 7 days of the Extension Phase only. The different dose levels were OXN50/25 mg PR, OXN60/30 mg PR, OXN70/35 mg PR and OXN80/40 mg PR twice daily. Titration up to the maximum daily dose of OXN90/45 mg PR twice daily was permitted from Visit 12 onwards. The different dose levels were OXN50/25 mg PR, OXN60/30 mg PR, OXN70/35 mg PR, OXN80/40 mg PR and OXN90/45 mg PR twice daily.

| Number of subjects in period 2^[1] | OXN PR (Extension) |
|---|---------------------------|
| Started | 195 |
| Completed | 167 |
| Not completed | 28 |
| Consent withdrawn by subject | 9 |
| Administrative | 1 |
| Adverse event, non-fatal | 16 |
| Lack of efficacy | 2 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only those subjects who completed the 5 week Double-blind Phase or who discontinued the Double-blind Phase prematurely due to constipation were eligible to enter the Extension Phase. Altogether almost all subjects who had completed the Double-blind Phase (195 of the 209 subjects) continued to the Extension Phase.

Baseline characteristics

Reporting groups

| | |
|---|------------|
| Reporting group title | Core study |
| Reporting group description: | |
| <p>This study was composed of three phases: a Pre-randomisation Phase, a Double-blind Phase and an Extension Phase. The Pre-randomisation Phase contained two periods: the Screening Period and the Run-in Period. The Screening Period involved prospective assessments and was designed to qualify subjects for participation in the Run-in Period. The Run-in Period was designed to titrate OxyPR to analgesic effect, qualify subjects for participation in the Double-blind Phase, e.g. confirm their constipation, and enable identification of a starting dose equivalent for the study medication to be used after randomisation. The Double-blind Phase was designed to demonstrate improvement in symptoms of constipation and non-inferiority in analgesic efficacy from OXN PR compared to subjects taking OxyPR tablets alone.</p> <p>This is the analysis of the core study, which summarises the results of the Pre-randomisation Phase and the Double-blind Phase.</p> | |

| Reporting group values | Core study | Total | |
|--|------------|-------|--|
| Number of subjects | 243 | 243 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 181 | 181 | |
| From 65-84 years | 60 | 60 | |
| 85 years and over | 2 | 2 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 143 | 143 | |
| Male | 100 | 100 | |

Subject analysis sets

| | |
|---|--|
| Subject analysis set title | Full analysis population |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| <p>Subjects who were randomised and received at least one dose of study medication during the Double-blind Phase and who had at least a one week Double-blind assessment of the primary efficacy variable, the BFI.</p> | |
| Subject analysis set title | Double-blind safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| <p>Subjects who received at least one dose of Double-blind study medication and had at least one safety assessment after that dose.</p> | |
| Subject analysis set title | Total exposure safety population (Extension phase) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects who received at least one dose of OXN PR in the Extension Phase and had at least one safety assessment after the first dose of extension phase study medication.

| | |
|----------------------------|---|
| Subject analysis set title | Received OXN PR during Double-blind phase (Extension Phase) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects who had received OXN PR in the Double-blind Phase, and who started the Extension Phase.

| | |
|----------------------------|--|
| Subject analysis set title | Received OxyPR during Double-blind phase (Extension phase) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects who had received OxyPR in the Double-blind Phase, and who started the Extension Phase.

| Reporting group values | Full analysis population | Double-blind safety population | Total exposure safety population (Extension phase) |
|--|--------------------------|--------------------------------|--|
| Number of subjects | 237 | 243 | 195 |
| 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) | 0 | 0 | 0 |
| Adults (18-64 years) | 178 | 181 | 150 |
| From 65-84 years | 58 | 61 | 44 |
| 85 years and over | 1 | 1 | 1 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 112 | 143 | 115 |
| Male | 77 | 100 | 80 |

| Reporting group values | Received OXN PR during Double-blind phase (Extension Phase) | Received OxyPR during Double-blind phase (Extension phase) | |
|--|---|--|--|
| Number of subjects | 100 | 95 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | | | |

| | | | |
|------|--|--|--|
| Male | | | |
|------|--|--|--|

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | OXN PR |
| Reporting group description: - | |
| Reporting group title | OxyPR |
| Reporting group description: - | |
| Reporting group title | OXN PR (Extension) |
| Reporting group description: Subjects who completed the 5 weeks Double-blind Phase, or subjects who discontinued the Double-blind Phase prematurely due to constipation, were eligible to enter the Extension Phase, which consisted of additional 24 weeks treatment with open-label OXN PR up to a maximum dose of OXN90/45 mg PR twice daily. | |
| Subject analysis set title | Full analysis population |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects who were randomised and received at least one dose of study medication during the Double-blind Phase and who had at least a one week Double-blind assessment of the primary efficacy variable, the BFI. | |
| Subject analysis set title | Double-blind safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects who received at least one dose of Double-blind study medication and had at least one safety assessment after that dose. | |
| Subject analysis set title | Total exposure safety population (Extension phase) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects who received at least one dose of OXN PR in the Extension Phase and had at least one safety assessment after the first dose of extension phase study medication. | |
| Subject analysis set title | Received OXN PR during Double-blind phase (Extension Phase) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects who had received OXN PR in the Double-blind Phase, and who started the Extension Phase. | |
| Subject analysis set title | Received OxyPR during Double-blind phase (Extension phase) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects who had received OxyPR in the Double-blind Phase, and who started the Extension Phase. | |

Primary: Improvement in Bowel Function Index

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|---|-------------------------------------|
| End point title | Improvement in Bowel Function Index |
| End point description: The BFI is a 3-term questionnaire to measure constipation from the patient's perspective. Study personnel asked the subject to rate ease of defecation, feeling of incomplete bowel evacuation and personal judgment of constipation in the last 7 days on a scale of 0 to 100, with lower numbers representing good and higher numbers representing poor bowel function. The BFI was assessed on Visit 1, 2 and 3 in the pre-randomisation Phase and on Visit 7,-10 in the Double-blind Phase. | |
| End point type | Primary |
| End point timeframe: Change in BFI from baseline at start of double-blind phase (Visit 3) to 5 weeks. | |

| End point values | OXN PR | OxyPR | Full analysis population | |
|--------------------------------------|-----------------|-----------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 104 | 101 | 205 | |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | -32.5 (± 26.96) | -14.2 (± 22.65) | -23.5 (± 26.52) | |

Statistical analyses

| Statistical analysis title | Superiority of OXN vs oxycodone (BFI improvement) |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

The objective of the analysis of BFI was to show that OXN PR is superior to OxyPR, using a one-tailed test at a 2.5% significance level.

The null hypothesis was that there is no difference between the treatment groups. The alternative hypothesis was that there is a difference between the treatment groups. A mixed model repeated measures analysis of covariance of the BFI was carried out for Weeks 1, 2, 4 and 5 as repeated measures.

| | |
|---|--------------------------------|
| Comparison groups | OxyPR v OXN PR |
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.001 |
| Method | Repeated measures analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -16.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.23 |
| upper limit | -9.86 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.14 |

Notes:

[1] - Full analysis population was used for this analysis.

Primary: Average pain over last 24 hours

| | |
|-----------------|---------------------------------|
| End point title | Average pain over last 24 hours |
|-----------------|---------------------------------|

End point description:

The subjects' average pain over the last 24 hours as measured by the Pain Intensity Scale (NRS 0-10), with 0 meaning no pain and 10 meaning worst imaginable pain.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Average pain over the last 24 hours at Week 5.

| End point values | OXN PR | OxyPR | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 94 | | |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | 3.6 (\pm 1.17) | 3.4 (\pm 1.32) | | |

Statistical analyses

| Statistical analysis title | Non-inferiority of OXN vs oxycodone (Average pain) |
|---|--|
| Statistical analysis description: | |
| The objective of the analysis of average pain over 24 hours was to show that OXN PR is non-inferior to OxyPR, using a one-tailed test at a 2.5% significance level. | |
| The null hypothesis was that the ratio between OXN PR and OxyPR in the 'Average Pain over the last 24 hours' is greater than or equal to 120%. The alternative hypothesis was that the ratio between OXN PR and OxyPR is lower than 120%. The change from baseline was analysed using a mixed model repeated measures analysis. | |
| Comparison groups | OXN PR v OxyPR |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.001 |
| Method | Repeated measures analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.99 |
| upper limit | -0.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.17 |

Other pre-specified: Improvement in Bowel Function Index (BFI) during Extension Phase

| | |
|---|--|
| End point title | Improvement in Bowel Function Index (BFI) during Extension Phase |
| End point description: | |
| The BFI is a 3-term questionnaire to measure constipation from the patient's perspective. Study personnel asked the subject to rate ease of defecation, feeling of incomplete bowel evacuation and personal judgment of constipation in the last 7 days on a scale of 0 to 100, with lower numbers representing good and higher numbers representing poor bowel function. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| The change in BFI from baseline (visit 11) to week 24 (visit 19) was assessed in the Extension Phase. | |

| End point values | OXN PR (Extension) | Total exposure safety population (Extension phase) | Received OXN PR during Double-blind phase (Extension Phase) | Received OxyPR during Double-blind phase (Extension phase) |
|--------------------------------------|-----------------------|--|--|---|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 164 | 164 | 85 | 79 |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | -18.9 (± 27.68) | -18.9 (± 27.68) | -8.3 (± 24.77) | -30.4 (± 26.15) |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Average pain over last 24 hours during Extension phase

| | |
|--|--|
| End point title | Average pain over last 24 hours during Extension phase |
| End point description: | |
| The subjects' average pain over the last 24 hours as measured by the Pain Intensity Scale (NRS 0-10), with 0 meaning no pain and 10 meaning worst imaginable pain. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Change in 'Average pain over the last 24 hours' from baseline (visit 11) to week 24 (visit 19). | |

| End point values | OXN PR (Extension) | Total exposure safety population (Extension phase) | Received OXN PR during Double-blind phase (Extension Phase) | Received OxyPR during Double-blind phase (Extension phase) |
|--------------------------------------|-----------------------|--|--|---|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 162 | 162 | 85 | 77 |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 1.35) | 0.1 (± 1.35) | 0.2 (± 1.3) | 0.1 (± 1.41) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs that occurred during the Double-blind Phase were those with an onset date on or after the first dose of Double-blind study medication up to and including 7 days after the last dose of study medication.

Adverse event reporting additional description:

Only treatment emergent AEs were included in the summary tables. A treatment emergent AE was defined as any AE (or worsening of an AE) with an onset date on or after the first dose of study medication . This also included AEs with an onset date up to and including 7 days after the last dose of study medication.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | OXN PR |
|-----------------------|--------|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Total exposure safety population (Extension phase) |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|-------|
| Reporting group title | OxyPR |
|-----------------------|-------|

Reporting group description:

Oxycodone prolonged-release

| Serious adverse events | OXN PR | Total exposure safety population (Extension phase) | OxyPR |
|---|-----------------|--|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 123 (2.44%) | 21 / 195 (10.77%) | 4 / 120 (3.33%) |
| number of deaths (all causes) | 1 | 4 | 3 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm malignant | | | |
| subjects affected / exposed | 2 / 123 (1.63%) | 2 / 195 (1.03%) | 3 / 120 (2.50%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 3 |
| Adenocarcinoma | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Lymphatic system neoplasm | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 2 / 195 (1.03%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Drug ineffective | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 195 (0.00%) | 0 / 120 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Coronary ostial stenosis | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 | | | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Tooth disorder | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth loss | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Myofascial pain syndrome | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Infections and infestations | | | |
| Bone abscess | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 195 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Cellulitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 195 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 195 (0.51%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | OXN PR | Total exposure safety population (Extension phase) | OxyPR |
|---|-------------------|--|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 67 / 123 (54.47%) | 128 / 195 (65.64%) | 57 / 120 (47.50%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 123 (1.63%) | 13 / 195 (6.67%) | 2 / 120 (1.67%) |
| occurrences (all) | 2 | 15 | 2 |
| General disorders and administration site conditions | | | |
| Pain | | | |
| subjects affected / exposed | 5 / 123 (4.07%) | 16 / 195 (8.21%) | 4 / 120 (3.33%) |
| occurrences (all) | 8 | 25 | 12 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 12 / 123 (9.76%) | 12 / 195 (6.15%) | 6 / 120 (5.00%) |
| occurrences (all) | 12 | 13 | 6 |
| Diarrhoea | | | |

| | | | |
|---|----------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 6 / 123 (4.88%) 9 | 15 / 195 (7.69%) 16 | 5 / 120 (4.17%) 5 |
| Constipation subjects affected / exposed occurrences (all) | 2 / 123 (1.63%) 2 | 12 / 195 (6.15%) 13 | 2 / 120 (1.67%) 2 |
| Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) | 8 / 123 (6.50%) 8 | 11 / 195 (5.64%) 12 | 3 / 120 (2.50%) 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported