

**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	v2
This version publication date	31 March 2016
First version publication date	12 August 2015
Version creation reason	• Changes to summary attachments add user

**Trial information****Trial identification**

Sponsor protocol code	OXN3506
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**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
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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
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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
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<b>Arm title</b>	OXN PR
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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

<b>Arm title</b>	OxyPR
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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.

<b>Number of subjects in period 1</b>	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

<b>Arm title</b>	OXN PR (Extension)
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### 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.

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Consent withdrawn by subject	9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

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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
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Reporting group description:

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.

This is the analysis of the core study, which summarises the results of the Pre-randomisation Phase and the Double-blind Phase.

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
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Subject analysis set type	Full analysis
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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
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Subject analysis set type	Safety analysis
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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)
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Subject analysis set type	Safety analysis
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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			
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## 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

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

<b>Statistical analysis title</b>	Superiority of OXN vs oxycodone (BFI improvement)
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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 <sup>[1]</sup>
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
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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
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End point timeframe:

Average pain over the last 24 hours at Week 5.

<b>End point values</b>	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

<b>Statistical analysis title</b>	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.	

<b>End point values</b>	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).

<b>End point values</b>	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
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

### Reporting groups

Reporting group title	OXN PR
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Reporting group description: -

Reporting group title	OxyPR
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Reporting group description:

Oxycodone prolonged-release

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

Serious adverse events	OXN PR	OxyPR	Total exposure safety population (Extension phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 123 (2.44%)	4 / 120 (3.33%)	21 / 195 (10.77%)
number of deaths (all causes)	1	3	4
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%)	3 / 120 (2.50%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 2
Adenocarcinoma			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lymphatic system neoplasm			

subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Prostate cancer			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug ineffective			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeling cold			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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 / 120 (0.00%)	0 / 195 (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
<b>Respiratory, thoracic and mediastinal disorders</b>			
Pleurisy			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Psychiatric disorders</b>			
Restlessness			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac disorders</b>			
Angina unstable			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary ostial stenosis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrasystoles			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Back pain			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myofascial pain syndrome			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
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			
Bone abscess			
subjects affected / exposed	0 / 123 (0.00%)	1 / 120 (0.83%)	0 / 195 (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
Bronchitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 120 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

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

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

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

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported