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.

Summary

EudraCT number	2010-021995-27
Trial protocol	GB CZ DE FI DK RO
Global end of trial date	10 February 2014

Results information

Result version number	v1
This version publication date	09 February 2016
First version publication date	12 August 2015

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, 0049 6431701453, info@contact-clinical-trial.com
Scientific contact	Clinical Trial Contact, Mundipharma Research GmbH & Co. KG, 0049 6431701453, 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	10 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2014
Global end of trial reached?	Yes
Global end of trial date	10 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

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 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 stabilised on 70 or 80 mg of OXN PR or OxyPR twice daily, the rescue dose of OxyIR would have been 25 mg.

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.

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	60
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

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	Overall trial (overall period)
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	Oxycodone-naloxone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Oxycodone-naloxone
Investigational medicinal product code	OXN
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	Oxycodone

Arm description:

Oxycodone prolonged-release

Arm type	Active comparator
Investigational medicinal product name	Oxycodone
Investigational medicinal product code	OXY
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	Oxycodone-naloxone	Oxycodone
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

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

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	Overall trial	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:

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	Per-protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects who received at least 4 weeks study medication during the Double-blind Phase and who sufficiently complied with the study protocol.

Reporting group values	Full analysis population	Double-blind safety population	Per-protocol population
Number of subjects	237	243	192
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)	178	181	
From 65-84 years	57	60	
85 years and over	2	2	
Gender categorical Units: Subjects			
Female		143	
Male		100	

End points

End points reporting groups

Reporting group title	Oxycodone-naloxone
Reporting group description: -	
Reporting group title	Oxycodone
Reporting group description:	
Oxycodone prolonged-release	
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	Per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects who received at least 4 weeks study medication during the Double-blind Phase and who sufficiently complied with the study protocol.	

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:	
From baseline at start of double-blind phase (Visit 3) to 5 weeks.	

End point values	Oxycodone-naloxone	Oxycodone	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 epeated measures analysis of covariance of the BFI was carried out for Weeks 1, 2, 4 and 5 as repeated measures.

Comparison groups	Oxycodone-naloxone v Oxycodone
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: Non-inferiority of OXN vs oxycodone (Average 24 hour pain)

End point title	Non-inferiority of OXN vs oxycodone (Average 24 hour pain)

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	Oxycodone-naloxone	Oxycodone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	94		
Units: Units				
arithmetic mean (standard deviation)	3.6 (± 1.17)	3.4 (± 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	Oxycodone-naloxone v Oxycodone
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

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	14.1

Reporting groups

Reporting group title	Oxycodone-naloxone
Reporting group description: -	
Reporting group title	Oxycodone
Reporting group description:	
Oxycodone prolonged-release	

Serious adverse events	Oxycodone-naloxone	Oxycodone	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 123 (2.44%)	4 / 120 (3.33%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	2 / 123 (1.63%)	3 / 120 (2.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 123 (0.81%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bone abscess			

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

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

Non-serious adverse events	Oxycodone-naloxone	Oxycodone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 123 (16.26%)	9 / 120 (7.50%)	
Nervous system disorders			
Hyperhidrosis			
subjects affected / exposed	8 / 123 (6.50%)	3 / 120 (2.50%)	
occurrences (all)	8	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 123 (9.76%)	6 / 120 (5.00%)	
occurrences (all)	12	6	

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