Clinical trial results:
A multicentre, double-blind, randomised, placebo controlled study to determine the efficacy and tolerability of OXN PR for the treatment of severe Parkinson's disease associated pain

Summary

EudraCT number	2011-002901-31
Trial protocol	GB ES DE CZ HU
Global end of trial date	05 November 2013

Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	OXN2504

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01439100
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	European Medical Operations, Mundipharma Research Limited, +44 122342490, info@contact-clinical-trials.com
Scientific contact	European Medical Operations, Mundipharma Research Limited, +44 122342490, info@contact-clinical-trials.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	05 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 November 2013
Global end of trial reached?	Yes
Global end of trial date	05 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of OXN PR compared to placebo with respect to analgesic efficacy in subjects with chronic severe pain associated with Parkinson's disease (PD), as assessed by averaged 24 hour pain scores collected for 7 days prior to the clinic visits.

Protection of trial subjects:

All subjects were provided with oral and written information describing the nature and duration of the study, its purpose, the procedures to be performed, the potential risks and benefits involved, and any potential discomfort. Each subject was given a copy of the patient information sheet (PIS) and informed consent form (ICF). The subject was asked to sign and date an ICF prior to any study-specific procedures being performed. Under a separate informed consent process, subjects were invited to consent to blood sampling for pharmacogenomic testing. The collected blood samples were anonymised and stored for future analysis. The consent to pharmacogenomic sampling was completely separate from the main study and subjects were able to take part in the main study without consenting to pharmacogenomic blood sampling. Blood sampling took place prior to receiving any dose of study medication.

Background therapy:

In the Double Blind period, Levodopa and benserazide hydrochloride combination Tablets, 100/25 mg, PRN, oral were provided as rescue medication.
In the Open Label period, Oxycodone immediate release (OxyIR) Capsules, 5 mg, PRN, oral were provided as rescue medication

Evidence for comparator:

The comparator product was placebo oxycodone hydrochloride and naloxone hydrochloride dihydrate combined oral prolonged release tablets, OXN PR. Placebo was chosen as comparator in order to measure the pain relief provided by the investigational medicinal product. Rescue medication (described above) was provided.

Actual start date of recruitment	31 October 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	Romania: 21
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Czech Republic: 33
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Poland: 35

Worldwide total number of subjects	202
EEA total number of subjects	202

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)	79
From 65 to 84 years	123
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 47 active centres in 7 countries: Czech Republic: 6 centres; Germany: 10 centres; Poland: 8 centres; Hungary: 7 centres; Romania: 3 centres; Spain: 7 centres; United Kingdom: 6 centres .

Pre-assignment

Screening details:

A total of 252 subjects provided written informed consent and were screened, 202 were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Oxycodone Naloxone

Arm description:

Oxycodone Naloxone Prolonged Release Tablets

Arm type	Experimental
Investigational medicinal product name	Oxycodone hydrochloride and naloxone hydrochloride dihydrate combined oral prolonged release tablets OXN PR-
Investigational medicinal product code	OXN
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OXN 5/2.5 mg PR; OXN 10/5 mg PR ; OXN 15/7.5 mg PR ; OXN 20/10 mg PR all taken q12h, Oral

Arm title	Placebo Oxycodone Naloxone

Arm description:

Placebo Oxycodone Naloxone Prolonged Release Tablets

Arm type	Placebo
Investigational medicinal product name	Placebo Oxycodone hydrochloride and naloxone hydrochloride dihydrate combined oral prolonged release tablets OXN PR-
Investigational medicinal product code	Placebo OXN
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo OXN 5/2.5 mg PR; Placebo OXN 10/5 mg PR ; Placebo OXN 15/7.5 mg PR ; Placebo OXN 20/10 mg PR all taken q12h, Oral

Number of subjects in period 1	Oxycodone Naloxone	Placebo Oxycodone Naloxone
Started	93	109
Completed	62	77
Not completed	31	32
Consent withdrawn by subject	6	6
Administrative	5	2
Adverse event, non-fatal	17	10
Lack of efficacy	3	14

Period 2

Period 2 title	Open Label
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label

Arms

Are arms mutually exclusive?	No
Arm title	Oxycodone Naloxone

Arm description:

Oxycodone Naloxone Prolonged Release Tablets

Arm type	Experimental
Investigational medicinal product name	Oxycodone hydrochloride and naloxone hydrochloride dihydrate combined oral prolonged release tablets OXN PR-
Investigational medicinal product code	OXN
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OXN 5/2.5 mg PR; OXN 10/5 mg PR ; OXN 15/7.5 mg PR ; OXN 20/10 mg PR all taken q12h, Oral

Arm title	Placebo Oxycodone Naloxone

Arm description:

Placebo Oxycodone Naloxone Prolonged Release Tablets

Arm type	Placebo
Investigational medicinal product name	Placebo Oxycodone hydrochloride and naloxone hydrochloride dihydrate combined oral prolonged release tablets OXN PR-
Investigational medicinal product code	Placebo OXN
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo OXN 5/2.5 mg PR; Placebo OXN 10/5 mg PR ; Placebo OXN 15/7.5 mg PR ; Placebo OXN 20/10 mg PR all taken q12h, Oral

Number of subjects in period 2	Oxycodone Naloxone	Placebo Oxycodone Naloxone
Started	64	87
Completed	63	82
Not completed	1	5
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Oxycodone Naloxone
Reporting group description:	
Oxycodone Naloxone Prolonged Release Tablets	
Reporting group title	Placebo Oxycodone Naloxone
Reporting group description:	
Placebo Oxycodone Naloxone Prolonged Release Tablets	

Reporting group values	Oxycodone Naloxone	Placebo Oxycodone Naloxone	Total
Number of subjects	93	109	202
Age categorical Units: Subjects			
18 to 60 years	20	20	40
>= 60 years and < 70 years	33	46	79
>= 70 years	40	43	83
Age continuous Units: years			
median	67	67.5	
full range (min-max)	46 to 83	49 to 85	-
Gender categorical Units: Subjects			
Female	49	51	100
Male	44	58	102

End points

End points reporting groups

Reporting group title	Oxycodone Naloxone
Reporting group description: Oxycodone Naloxone Prolonged Release Tablets	
Reporting group title	Placebo Oxycodone Naloxone
Reporting group description: Placebo Oxycodone Naloxone Prolonged Release Tablets	
Reporting group title	Oxycodone Naloxone
Reporting group description: Oxycodone Naloxone Prolonged Release Tablets	
Reporting group title	Placebo Oxycodone Naloxone
Reporting group description: Placebo Oxycodone Naloxone Prolonged Release Tablets	

Primary: To demonstrate superiority of OXN PR compared to placebo with respect to analgesic efficacy in subjects with chronic severe pain associated with Parkinson's disease (PD), as assessed by averaged 24 hour pain scores collected for 7 days prior to the clinic

End point title	To demonstrate superiority of OXN PR compared to placebo with respect to analgesic efficacy in subjects with chronic severe pain associated with Parkinson's disease (PD), as assessed by averaged 24 hour pain scores collected for 7 days prior to the clinic

End point description:

There were no plans to make adjustments for multiplicity for the primary endpoint. There was only one primary endpoint for this study, the averaged 24 hour pain scores collected for 7 days prior to the study clinical visit at Week 16. All other analyses on the primary endpoint for different populations and methods of handling missing data are conducted as sensitivity analyses.

End point type	Primary

End point timeframe:

The averaged 24 hour pain scores collected for 7 days prior to the study clinical visit at Week 16

End point values	Oxycodone Naloxone	Placebo Oxycodone Naloxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	73		
Units: Pain Scale				
number (confidence interval 95%)	5 (4.48 to 5.45)	5.6 (5.14 to 6.03)		

Statistical analyses

Statistical analysis title	Superiority of OXN PR vs Placebo (ave 24h pain)

Statistical analysis description:

The primary analysis to assess the statistical hypothesis was via a Mixed Model for Repeated Measures (MMRM) analysis. The comparison was used to test, in a confirmatory manner, the hypothesis that OXN PR was superior to placebo with respect to the averaged 24 hour pain scores following at Week 16 i.e. to test the following 2-sided hypothesis:
Null hypothesis: OXN PR = Placebo in averaged 24 hour pain scores at Week 16
Alternative: OXN PR ≠ Placebo in averaged 24 hour pain scores at Week 16

Comparison groups	Oxycodone Naloxone v Placebo Oxycodone Naloxone
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.058
Method	Mixed Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[1] - Superiority was demonstrated if the primary comparison of OXN PR versus Placebo was significant at the 5% level.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In the Double-blind period the OXN PR group mean exposure was 90.8 days, as compared with 93.1 days in the placebo group. In the Open Label period the mean exposure was 28.7 days

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Oxycodone Naloxone

Reporting group description:

Oxycodone Naloxone Prolonged Release Tablets - Double Blind Period

Reporting group title	Placebo Oxycodone Naloxone

Reporting group description:

Placebo Oxycodone Naloxone Prolonged Release Tablets - Double blind period

Serious adverse events	Oxycodone Naloxone	Placebo Oxycodone Naloxone	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 92 (5.43%)	7 / 109 (6.42%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hypertrophy			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pyelocaliectasis			

subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 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	Placebo Oxycodone Naloxone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 92 (65.22%)	76 / 109 (69.72%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 92 (5.43%)	3 / 109 (2.75%)	
occurrences (all)	6	3	
Nervous system disorders			
Somnolence			
subjects affected / exposed	12 / 92 (13.04%)	15 / 109 (13.76%)	
occurrences (all)	18	16	
Dizziness			
subjects affected / exposed	12 / 92 (13.04%)	12 / 109 (11.01%)	
occurrences (all)	18	21	
Headache			
subjects affected / exposed	6 / 92 (6.52%)	9 / 109 (8.26%)	
occurrences (all)	7	10	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 92 (7.61%)	10 / 109 (9.17%)	
occurrences (all)	8	13	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	6 / 92 (6.52%)	4 / 109 (3.67%)	
occurrences (all)	6	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	18 / 92 (19.57%)	13 / 109 (11.93%)	
occurrences (all)	30	19	

Constipation			
subjects affected / exposed	16 / 92 (17.39%)	6 / 109 (5.50%)	
occurrences (all)	20	6	
Dry mouth			
subjects affected / exposed	5 / 92 (5.43%)	5 / 109 (4.59%)	
occurrences (all)	6	6	
Vomiting			
subjects affected / exposed	7 / 92 (7.61%)	3 / 109 (2.75%)	
occurrences (all)	11	3	
Diarrhoea			
subjects affected / exposed	2 / 92 (2.17%)	7 / 109 (6.42%)	
occurrences (all)	2	7	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	7 / 92 (7.61%)	2 / 109 (1.83%)	
occurrences (all)	8	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2012	In Section 8.3.2 'Secondary Efficacy Variable(s)' a bullet point was added between bullet 1 and 3 that the percentage of responders (defined as a ≥30% reduction from baseline) in averaged 24 hour pain scores collected for 7 days preceding the study clinic visit at Week 16 was also tested in a hierarchical testing strategy. In Section 14.2 'Statistical Considerations', the percentage of responders in averaged 24 hour pain scores at Week 16 was added to the key secondary endpoints which were tested for confirmatory statistical significance under a hierarchical testing strategy. In Section 14.7 'Secondary Outcome/Efficacy Variables, it was added that in the case the analyses described before in this section yielded statistically significant differences at each time point, the percentage of responders in averaged 24 hour pain scores at Week 16 were analysed in a formal, confirmatory manner to test for superiority. Logistic regression analysis was used to determine the odds ratio and 95% confidence interval of OXN PR relative to placebo. The statistical model included terms for treatment and centre as factors, and baseline averaged pain score as a covariate. LOCF was used for this analysis. A supportive analysis was performed on the PP Population. A sensitivity analysis on the FAP was also applied to the analysis of the key secondary endpoint of the percentage of responders in averaged 24 hour pain scores, implementing the same logistic regression model, using OC data at the 16-week time point. The analysis of the key secondary endpoint, CGI-I (as assessed by the Investigator), were conducted in a formal manner in the event that the hierarchical testing structure yielded statistically significant differences at each time point. A statistically significant difference in the percentage of responders in averaged 24 hour pain scores at Week 16 was added as a criterion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported