Clinical trial results:
A Randomized, Double-blind, Double-dummy, Placebo-controlled, Active-controlled, Parallel-group, Multicenter Trial of Oxycodone/Naloxone Controlled-release Tablets (OXN) to Assess the Analgesic Efficacy (Compared to Placebo) and the Management of Opioid-induced Constipation (Compared to Oxycodone Controlled-release Tablets [OXY]) in Opioid-experienced Subjects With Uncontrolled Moderate to Severe Chronic Low Back Pain and a History of Opioid-induced Constipation Who Require Around-the-clock Opioid Therapy

Summary

EudraCT number	2011-005060-26
Trial protocol	CZ PL IT
Global end of trial date	02 October 2014

Results information

Result version number	v1 (current)
This version publication date	28 April 2016
First version publication date	28 April 2016

Trial information

Trial identification

Sponsor protocol code	ONU3704

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01427270
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Purdue Pharma LP
Sponsor organisation address	One Stamford Forum, Stamford, United States, CT 06901-3431
Public contact	Clinical Leader, Purdue Pharma LP, 1 800-733-1333,
Scientific contact	Clinical Leader, Purdue Pharma LP, 1 800-733-1333,

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	02 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2014
Global end of trial reached?	Yes
Global end of trial date	02 October 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of OXN for the management of opioid-induced constipation (OIC) compared with OXY in subjects with moderate to severe low back pain and OIC who require around-the clock opioid therapy.

Protection of trial subjects:

Patient protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator:

The results of clinical studies conducted thus far indicated that the administration of OXN was well-tolerated and had similar analgesic efficacy compared with OXY alone, with significantly improved bowel function. OXN tablets were therefore compared to OXY tablets for the management of OIC.

Actual start date of recruitment	29 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 54
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	United States: 1947
Worldwide total number of subjects	2029
EEA total number of subjects	82

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)	1763
From 65 to 84 years	260
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

First subject first visit: 29-Aug-2011; last subject last visit: 02-Oct-2014. The study was conducted at 174 medical/research sites in the United States, 1 site in Italy, 11 sites in the Czech Republic, and 7 sites in Poland.

Pre-assignment

Screening details:

Opioid-experienced subjects with uncontrolled moderate to severe chronic low back pain and a history of OIC, who required around-the-clock opioid therapy.

Pre-assignment period milestones

Number of subjects started	2029
Number of subjects completed	908

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Enrolled but did not enter OLT Period: 1109
Reason: Number of subjects	Enrolled in OLT Period but did not take Study Drug: 12

Period 1

Period 1 title	Open-label Titration Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-label Titration OXY

Arm description:

Oxycodone HCl controlled-release tablets (OXY 10, 20, 30, or 40 mg), taken orally every 12 hours (q12h) for up to 28 days during the open-label titration period.

Arm type	Open-Label Titration Period
Investigational medicinal product name	OXY
Investigational medicinal product code	OXY
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received OXY tablets orally q12h

Number of subjects in period 1[1]	Open-label Titration OXY
Started	908
Completed	451
Not completed	457
Adverse event, serious fatal	1
Consent withdrawn by subject	58

Confirmed or suspected diversion	20
Administrative	22
Did not qualify	246
Adverse event, non-fatal	52
Lost to follow-up	12
Lack of efficacy	46

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 2029 subjects were enrolled in the trial overall. 908 subjects started the open-label titration period (Period 1 [baseline period]). 451 subjects completed the baseline period and were randomized to the double-blind period (2 subjects were randomized but were not included in the randomized safety population as they did not report taking any double-blind study drug). The numbers are therefore correct according to the particular populations used to report the baseline and double-blind periods.

Period 2

Period 2 title	Double-blind Period
Is this the baseline period?	No
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 of the study, the subject and all personnel involved with the conduct, analysis and interpretation of the study, including the investigators, study site personnel, and the sponsor (or designee) staff, were blinded to study drug codes. The randomization schedule was kept strictly confidential and was accessible only to authorized persons per the sponsor's Standard Operating Procedures until the time of unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	OXN Group

Arm description:

Oxycodone/Naloxone controlled-release tablets (OXN 10/5 - 40/20 mg), taken orally q12h for up to 12 weeks during the double-blind period.

Arm type	Experimental
Investigational medicinal product name	OXN
Investigational medicinal product code	OXN
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received OXN tablets orally q12h

Arm title	OXY Group

Arm description:

Oxycodone HCl controlled-release tablets (OXY 10 - 40 mg), taken orally q12h for up to 12 weeks during the double-blind period.

Arm type	Active comparator
Investigational medicinal product name	OXY
Investigational medicinal product code	OXY
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received OXY tablets orally q12h

Arm title	Placebo Group

Arm description:

Placebo tablets to match OXN or OXY, taken orally q12h for up to 12 weeks during the double-blind period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo tablets to match OXN or OXY orally q12h

Number of subjects in period 2	OXN Group	OXY Group	Placebo Group
Started	150	152	149
Completed	121	112	96
Not completed	29	40	53
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	5	7	10
Confirmed or suspected diversion	1	3	5
Administrative	2	8	6
Adverse event, non-fatal	10	11	10
Lost to follow-up	2	4	2
Lack of efficacy	9	7	19

Baseline characteristics

Reporting groups	
Reporting group title	Open-label Titration OXY
Reporting group description:	
Oxycodone HCl controlled-release tablets (OXY 10, 20, 30, or 40 mg), taken orally every 12 hours (q12h) for up to 28 days during the open-label titration period.	

Reporting group values	Open-label Titration OXY	Total	
Number of subjects	908	908	
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)	771	771	
From 65-84 years	132	132	
85 years and over	5	5	
Age Continuous Units: years			
arithmetic mean	52.9		
standard deviation	± 11.89	-	
Gender Categorical Units: Subjects			
Male	350	350	
Female	558	558	

End points

End points reporting groups

Reporting group title	Open-label Titration OXY
Reporting group description:	
Oxycodone HCl controlled-release tablets (OXY 10, 20, 30, or 40 mg), taken orally every 12 hours (q12h) for up to 28 days during the open-label titration period.	
Reporting group title	OXN Group
Reporting group description:	
Oxycodone/Naloxone controlled-release tablets (OXN 10/5 - 40/20 mg), taken orally q12h for up to 12 weeks during the double-blind period.	
Reporting group title	OXY Group
Reporting group description:	
Oxycodone HCl controlled-release tablets (OXY 10 - 40 mg), taken orally q12h for up to 12 weeks during the double-blind period.	
Reporting group title	Placebo Group
Reporting group description:	
Placebo tablets to match OXN or OXY, taken orally q12h for up to 12 weeks during the double-blind period.	

Primary: Overall Complete Spontaneous Bowel Movement (CSBM) Responder Rates

End point title	Overall Complete Spontaneous Bowel Movement (CSBM) Responder Rates
End point description:	
A subject was an overall CSBM responder if the subject was a monthly responder (that is, for at least 3 out of 4 weeks in that month the subject had ≥ 3 CSBMs/week and an increase from baseline of ≥ 1 CSBM/week for that week) for all 3 months of the double-blind period. A CSBM was a spontaneous bowel movement that was accompanied by the subject self-reporting a feeling of complete evacuation.	
End point type	Primary
End point timeframe:	
Weeks 1 through 12	

End point values	OXN Group	OXY Group	Placebo Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	151	148	
Units: Responder Rate (percentage responders)				
number (not applicable)	12	4	10.1	

Statistical analyses

Statistical analysis title	Treatment Comparison, OXN vs OXY
Comparison groups	OXY Group v OXN Group

Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0071 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - One-sided right-tailed p-value of the treatment effect (OXN vs OXY) adjusted for interim analysis treatment effect using an inverse normal combination method.
[2] - P-value was compared to a significance level of 0.0245.

Secondary: CSBM Responder at Least 50% of the Weeks in the Double-blind Period

End point title	CSBM Responder at Least 50% of the Weeks in the Double-blind Period

End point description:

A subject was a weekly CSBM responder for at least 50% of the weeks if the subject had ≥ 3 CSBMs/week and an increase from baseline of ≥ 1 CSBM/week for that week for at least 6 out of the 12 weeks of the double-blind period.

End point type	Secondary

End point timeframe:

Weeks 1 through 12

End point values	OXN Group	OXY Group	Placebo Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	151	148	
Units: participants (responders)	43	22	27	

Statistical analyses

Statistical analysis title	Treatment Comparison, OXN vs OXY
Comparison groups	OXN Group v OXY Group
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0031
Method	Cochran-Mantel-Haenszel

Notes:

[3] - Treatment effect (difference between OXN and OXY) was assessed based on the Cochran-Mantel-Haenszel test stratified for the randomization dose group (2-sided)

Secondary: Laxative-free Responder at Least 50% of the Weeks in the Double-blind Period

End point title	Laxative-free Responder at Least 50% of the Weeks in the Double-blind Period

End point description:

A subject was a weekly laxative-free responder for at least 50% of the weeks if the subject was a weekly CSBM responder and took no laxatives in a given week for at least 6 out of the 12 weeks of the double-blind period.

End point type	Secondary

End point timeframe:
Weeks 1 through 12

End point values	OXN Group	OXY Group	Placebo Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	151	148	
Units: participants (responders)	37	18	22	

Statistical analyses

Statistical analysis title	Treatment Comparison, OXN vs OXY
Comparison groups	OXN Group v OXY Group
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0044
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Treatment effect (difference between OXN and OXY) was assessed based on the Cochran-Mantel-Haenszel test stratified for the dose level used as a stratification factor for randomization (2-sided).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from start of study participation through the period beyond study completion. AEs are presented for subjects in the safety population (N = 908).

Adverse event reporting additional description:

AEs were learned of through spontaneous reports and/or subject interview, or were observed during physical examinations or other safety assessments. Ongoing AEs were followed until resolution or 30 days after last study drug dose. Serious AEs up to 30 days following the last study visit were followed until the AE or sequelae resolved or stabilized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Open-label Titration OXY

Reporting group description:

Oxycodone HCl controlled-release tablets (OXY 10, 20, 30, or 40 mg), taken orally every 12 hours (q12h) for up to 28 days during the open-label titration period.

Reporting group title	OXN Group

Reporting group description:

Oxycodone/Naloxone controlled-release tablets (OXN 10/5 - 40/20 mg), taken orally q12h for up to 12 weeks during the double-blind period.

Reporting group title	OXY Group

Reporting group description:

Oxycodone HCl controlled-release tablets (OXY 10 - 40 mg), taken orally q12h for up to 12 weeks during the double-blind period.

Reporting group title	Placebo Group

Reporting group description:

Placebo tablets to match OXN or OXY, taken orally q12h for up to 12 weeks during the double-blind period.

Serious adverse events	Open-label Titration OXY	OXN Group	OXY Group
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 908 (2.09%)	5 / 150 (3.33%)	11 / 151 (7.28%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Head and neck cancer			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Abortion induced			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (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
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	2 / 908 (0.22%)	0 / 150 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 908 (0.00%)	1 / 150 (0.67%)	0 / 151 (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
Psychiatric disorders			
Drug abuse			
subjects affected / exposed	5 / 908 (0.55%)	1 / 150 (0.67%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	0 / 5	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance abuse			
subjects affected / exposed	3 / 908 (0.33%)	1 / 150 (0.67%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Drug screen positive			
subjects affected / exposed	1 / 908 (0.11%)	1 / 150 (0.67%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Concussion			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 908 (0.00%)	1 / 150 (0.67%)	0 / 151 (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 failure congestive			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (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
Myocardial infarction			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (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

Cerebrovascular accident			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (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
Convulsion			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (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
Toxic encephalopathy			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 908 (0.11%)	1 / 150 (0.67%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (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

Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (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
Lumbar spinal stenosis			
subjects affected / exposed	1 / 908 (0.11%)	0 / 150 (0.00%)	0 / 151 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 908 (0.00%)	0 / 150 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 148 (4.73%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Head and neck cancer			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Drug abuse			
subjects affected / exposed	4 / 148 (2.70%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Substance abuse			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Drug screen positive			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury			

subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Overdose				
subjects affected / exposed	0 / 148 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	0 / 148 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 148 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 148 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid artery stenosis				
subjects affected / exposed	0 / 148 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 148 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				

subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxic encephalopathy			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lumbar spinal stenosis			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 148 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Open-label Titration OXY	OXN Group	OXY Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 908 (6.83%)	19 / 150 (12.67%)	26 / 151 (17.22%)
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 908 (1.76%)	8 / 150 (5.33%)	7 / 151 (4.64%)
occurrences (all)	17	8	8
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	46 / 908 (5.07%)	11 / 150 (7.33%)	12 / 151 (7.95%)
occurrences (all)	51	12	13
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 908 (0.77%)	3 / 150 (2.00%)	9 / 151 (5.96%)
occurrences (all)	7	3	9

Non-serious adverse events	Placebo Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 148 (10.81%)		

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 7 / 148 (4.73%) 7		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 6 / 148 (4.05%) 6		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 4 / 148 (2.70%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2011	•Screening period extended to 14 days since the urine drug test might require 7 days. •The Food and Drug Administration (FDA) recommended analgesic medications to be thoroughly documented after study drug discontinuation, including: Subjects asked to record daily in a separate diary the intake of analgesic medications and study site collection of diary. •Inclusion of conversion ratios of Tapentadol to morphine and Buprenorphine (Butrans®) to morphine (approved by FDA in 2008 and 2010, respectively) in the conversion table in the protocol. •Use of 'prokinetic drug' not permitted in this study. •More diary recordings (modified Subjective Opiate Withdrawal Scale [SOWS] before visit 5, rescue medication for constipation) at the time of study drug discontinuation. Bowel function measures to be recorded at time of study drug discontinuation (SDD). Modified SOWS always recorded in the diary daily from visit 3 until visit 5 during the double-blind period.
13 December 2011	•FDA recommended the eligibility criteria be modified by standardizing the definition and diagnoses of OIC rather than OIC criteria being defined by the investigator. •Efficacy variables and statistical methods were adjusted based on FDA comments on the protocol. •Screening period was extended to 21 days since urine drug confirmatory test could require 10 business days. •Due to scheduling issues, the language for open-label titration (OLT) period was updated to reflect 'up to 28 days for qualification' and 'up to 31 days for visit 3 for scheduling purpose'. •Electrocardiogram (ECG) criteria for study (or study drug) discontinuation were modified based on other sponsor programs. •Instructions to clarify the procedures when 2 visits (unscheduled SDD visit and a regularly scheduled visit, or unscheduled SDD follow-up visit and a regularly scheduled visit) coincided. •Based on recruitment, the number of study centers was increased.
20 June 2012	•Additional items were included in the electronic diary assessing bowel function. This was in order to capture relevant gastrointestinal (GI) symptoms using a validated scale and to ensure GI symptoms were captured on a daily basis. •Subjects were allowed to take OxyIR® up to 2 pills daily (rather than 1 pill up to 2 times, at least 4 hours apart) during the double-blind period. This matched the use of OxyIR® during the 7 days of the OLT period used to qualify the subject. •Two exclusion criteria related to nerve/plexus blocks were changed, neuroablation and neurosurgical procedures for pain control. •The primary analysis for "average pain over the last 24 hours" variable was changed from a pattern mixture model including the use of data from retrieved dropouts to the same analysis without using data from retrieved dropouts. The rationale for the change was to address FDA concerns regarding the use of retrieved dropout data. •Pharmacogenomic sampling was changed.

27 March 2013	●To enhance enrollment, low back pain criteria was changed (low back pain with radiation below the knee was now allowed) and rescreening was allowed with medical monitor approval. ●Clarified exclusion criterion regarding neuropathic pain conditions. ●Clarified restrictions for nerve stimulators and intraspinal pain pumps. ●To enhance enrollment and facilitate entry into the double-blind period, OIC entry criteria was changed and the primary OIC variable was changed correspondingly. ●To facilitate entry into the double-blind period, the double-blind entry criterion requiring number of consecutive days of a stable dose of OXY was changed from 9 to 7. ●To accommodate time required to confirm positive urine drug tests at screening, the screening period was extended from 21 days to 28 days. ●Additional categories of medically qualified individuals were allowed to perform physical examinations. ●The time between replicate ECG measurements was reduced from 10 minutes to 5 minutes.
09 September 2013	●Due to slow subject recruitment and a change in sponsor rationale for planning sample size for the overall CSBM responder rate, the following changes were made: Sample of 200 subjects per treatment arm was thought to be sufficient for assessment of CSBM responder rate, but an interim analysis was deemed necessary in order to know whether the sample size needed adjustment, and Since 200 subjects per treatment arm were not thought to be sufficient for assessment of analgesia, the previously specified primary and secondary analgesia endpoints were specified as other endpoints for the study and a pooled analysis of the data from trials ONU3704 and ONU3705 was planned for the analgesia efficacy endpoints. Study objective on analgesic efficacy was changed from a primary objective to a secondary objective. Analgesic efficacy variable, "average pain over the last 24 hours", was changed from a primary efficacy variable to other efficacy variable. Analgesic efficacy variables, Medical Outcomes Study-Sleep Scale, and Patient Global Impression of Change were changed from secondary efficacy variables to other efficacy variables. Analysis for the primary and secondary efficacy variables were adjusted accordingly. ●To enhance enrollment, investigator centers were increased from 150 sites to 200 sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Enrollment was stopped before reaching 200 per treatment group for business reasons and not due to efficacy or safety. At that time, the number of subjects randomized to double-blind was about 150 per treatment group (75% of planned sample size).

Notes: