Clinical trial results:
A randomised, double-blind, double-dummy, cross-over multicenter study to demonstrate equivalence in analgesic efficacy and bowel function taking oxycodone equivalents of 120 and 160 mg per day as achieved with the higher OXN PR tablet strengths (OXN60/30 mg PR, OXN80/40 mg PR) twice daily compared to the identical daily dose taken as a combination of lower tablet strengths in subjects with non-malignant or malignant pain that requires around-the-clock opioid therapy.

Summary

EudraCT number	2013-004888-31
Trial protocol	GB CZ IT ES
Global end of trial date	26 July 2016

Results information

Result version number	v1
This version publication date	11 March 2017
First version publication date	11 March 2017

Trial information

Trial identification

Sponsor protocol code	OXN3508

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02321397
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 GmbH & Co KG, +44 1223424900, info@contact-clinical-trials.com
Scientific contact	European Medical Operations, Mundipharma Research GmbH & Co KG, +44 1223424900, 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	22 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2016
Global end of trial reached?	Yes
Global end of trial date	26 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:
To demonstrate equivalence between multiple lower strength OXN PR tablets and a single higher strength OXN PR tablet taken at the same overall total daily dose as shown by:
• Analgesic efficacy based on the mean of subjects' 'Average Pain over the last 24 hours' at the last 2 visits of each Cross-over Period, as assessed by the Pain Intensity Scale.
Co-primary objective:
• Equivalent bowel function as assessed by the Bowel Function Index (BFI).

Protection of trial subjects:

Protection of trial subjects:
1) Inclusion criteria:
- Male or female subjects at least 18 years (females less than one year post-menopausal had to have a negative serum or urine pregnancy test prior to the first dose of study treatment, be non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study. A highly effective method of birth control was defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (Intrauterine Device, hormonal), sexual abstinence or vasectomised partner).
- Subjects had to be willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medication, completion of subjective evaluations, attending scheduled clinic visits, completing telephone contacts, and compliance with protocol requirements as evidenced by providing written, informed consent.
2) Exclusion criteria:
- Several exclusion criteria excluded subjects who were at risk from the use of IMP (e.g. those with hypersensitivity) or the study methods (please refer to protocol)
3) Dose discontinuation:
The Investigator(s) or subjects themselves were able to stop study treatment at any time for safety or personal reasons.
Investigators were to discontinue a subject from study treatment if the subject demonstrated opioid withdrawal, had an SAE due to an opioid withdrawal syndrome, had Markedly Abnormal Laboratory values or abnormal vital signs or vigilance impairment fulfilling at least one SAE criterion, or required more than 160/80 mg OXN per day.
4) Safety assessments consisted of monitoring and recording all AEs and SAEs, observed or volunteered, regardless of suspected causal relationship to the IMP. This included reactions, interactions, accidents, illnesses, misuse, abuse, lab values, vital signs, ECG, vigilance and SOWS.

Background therapy:

Rescue medication: Oxycodone immediate release capsules. Analgesic rescue medication may have been dosed no sooner than every 4 hours as needed. 6 analgesic rescue doses were the total maximum amount of analgesic rescue medication per day (on single occasions).
The analgesic rescue medication dose was approximately 1/6th the total daily maintenance dose. For a subject stabilised on OXN60/30 mg PR twice daily (HST or LST), the rescue dose of OxyIR would have been 20 mg; for a subject stabilised on OXN80/40 mg PR twice daily (HST or LST), the rescue dose of OxyIR would have been 25 mg.
Subjects, who consistently (i.e. ≥ 3 days per week) required more than 2 rescue doses per day of OxyIR were discontinued.

Evidence for comparator: -	
Actual start date of recruitment	27 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Czech Republic: 70
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	217
EEA total number of subjects	217

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)	149
From 65 to 84 years	65
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study was conducted a total of 40 sites in 6 countries (8 sites in the Czech Republic, 15 in Germany, 4 in Italy, 4 in Poland, 4 in Spain, 5 in the United Kingdom). In addition, 16 sites did not recruit subjects (1 in the Czech Republic, 2 in Germany, 5 in Spain, 5 in the UK, 1 in Italy and 2 in Poland).

Pre-assignment

Screening details:

Screening period: up to 2 weeks, Run-in Phase: 1-4 weeks. Subjects who did not comply with all screening inclusion and exclusion criteria or withdrew their consent prior to entering the Run-In Period were considered Screening Failures. The Run-In Period served to qualify the subject for entry into the Double-blind Phase.

Pre-assignment period milestones

Number of subjects started	217
Intermediate milestone: Number of subjects	Run-in Period: 195
Number of subjects completed	155[1]

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 22
Reason: Number of subjects	Adverse event, non-fatal: 17
Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Did not meet Double-blind Phase inclusion criteria: 16
Reason: Number of subjects	Lack of therapeutic effect: 4

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.
Justification: This study was done in a cross-over design. Subjects received both, low and high strength tablets within their respective dosing group.

Period 1

Period 1 title	Double-blind Period (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

Arms

Are arms mutually exclusive?	No
Arm title	OXN80/40 PR LST

Arm description:

Subjects who received OXN Low Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

Arm type	Active comparator
Investigational medicinal product name	Oxycodone/naloxone 80/40 mg low strength tablets
Investigational medicinal product code	OXN80/40 LST
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2x 40/20 mg oxycodone/naloxone combination twice daily. Total daily dose: 160mg/80mg oxycodone/naloxone

Arm title	OXN80/40 PR HST

Arm description:

Subjects who received OXN High Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

Arm type	Experimental
Investigational medicinal product name	Oxycodone/naloxone 80/40 mg high strength tablets
Investigational medicinal product code	OXN80/40 HST
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

80/40 mg oxycodone/naloxone combination twice daily. Total daily dose: 160mg/80mg oxycodone/naloxone

Arm title	OXN60/30 PR LST

Arm description:

Subjects who received OXN Low Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

Arm type	Active comparator
Investigational medicinal product name	Oxycodone/naloxone 60/30 mg low strength tablets
Investigational medicinal product code	OXN60/30 LST
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20/10 and 40/20 mg oxycodone/naloxone combination twice daily. Total daily dose: 120mg/60mg oxycodone/naloxone

Arm title	OXN60/30 PR HST

Arm description:

Subjects who received OXN High Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

Arm type	Experimental
Investigational medicinal product name	Oxycodone/naloxone 60/30 mg high strength tablets
Investigational medicinal product code	OXN60/30 HST
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60/30 mg oxycodone/naloxone combination twice daily. Total daily dose: 120mg/60mg oxycodone/naloxone

Number of subjects in period 1	OXN80/40 PR LST	OXN80/40 PR HST	OXN60/30 PR LST
Started	79	76	75
Interim analysis	20 [2]	20 [3]	20 [4]
Completed	75	73	72
Not completed	4	3	3
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	-	2	1
Adverse event, non-fatal	2	-	2
Lack of efficacy	1	1	-

Number of subjects in period 1	OXN60/30 PR HST
Started	73
Interim analysis	20 [5]
Completed	73
Not completed	0
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Lack of efficacy	-

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The interim analysis was only done with a fraction of the subjects who took part in the study.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The interim analysis was only done with a fraction of the subjects who took part in the study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The interim analysis was only done with a fraction of the subjects who took part in the study.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The interim analysis was only done with a fraction of the subjects who took part in the study.

Baseline characteristics

Reporting groups[1]	
Reporting group title	OXN80/40 PR LST
Reporting group description:	
Subjects who received OXN Low Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.	
Reporting group title	OXN80/40 PR HST
Reporting group description:	
Subjects who received OXN High Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.	
Reporting group title	OXN60/30 PR LST
Reporting group description:	
Subjects who received OXN Low Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.	
Reporting group title	OXN60/30 PR HST
Reporting group description:	
Subjects who received OXN High Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline period started after Screening and Run-In Period. Therefore subjects who dropped out during screening and run-in are not included in the population of the baseline period.

Reporting group values	OXN80/40 PR LST	OXN80/40 PR HST	OXN60/30 PR LST
Number of subjects	79	76	75
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			
Age continuous Units: years			
arithmetic mean	56.7	56.7	56.9
standard deviation	± 10.7	± 10.78	± 11.62
Gender categorical Units: Subjects			
Female	38	38	44
Male	41	38	31

Reporting group values	OXN60/30 PR HST	Total	
Number of subjects	73	155	

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			
Age continuous Units: years			
arithmetic mean	56.8		
standard deviation	± 11.76	-	
Gender categorical Units: Subjects			
Female	44	83	
Male	29	72	

End points

End points reporting groups

Reporting group title	OXN80/40 PR LST
Reporting group description:	
Subjects who received OXN Low Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.	
Reporting group title	OXN80/40 PR HST
Reporting group description:	
Subjects who received OXN High Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.	
Reporting group title	OXN60/30 PR LST
Reporting group description:	
Subjects who received OXN Low Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.	
Reporting group title	OXN60/30 PR HST
Reporting group description:	
Subjects who received OXN High Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.	
Subject analysis set title	OXN80/40 LST PPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Per Protocol Population OXN80/40 LST treatment group	
Subject analysis set title	OXN80/40 HST PPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Per Protocol Population OXN80/40 HST treatment group	
Subject analysis set title	OXN60/30 HST PPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Per Protocol Population OXN60/30 HST treatment group	
Subject analysis set title	OXN60/30 LST PPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Per Protocol Population OXN60/30 LST treatment group	
Subject analysis set title	Total PPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Total per protocol population	
Subject analysis set title	OXN80/40 LST FAP
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Population OXN80/40 LST treatment group	
Subject analysis set title	OXN80/40 HST FAP
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Population OXN80/40 HST treatment group	
Subject analysis set title	OXN60/30 HST FAP
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Population OXN60/30 HST treatment group	
Subject analysis set title	OXN60/30 LST FAP

Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Population OXN60/30 LST treatment group	
Subject analysis set title	Total FAP
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Population total	
Subject analysis set title	OXN80/40 LST Interim
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects receiving OXN80/40 LST in the interim analysis	
Subject analysis set title	OXN80/40 HST Interim
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects receiving OXN80/40 HST in the interim analysis	
Subject analysis set title	OXN60/30 HST Interim
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects receiving OXN60/30 HST in the interim analysis	
Subject analysis set title	OXN60/30 LST Interim
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects receiving OXN60/30 LST in the interim analysis	
Subject analysis set title	Interim total
Subject analysis set type	Sub-group analysis
Subject analysis set description: Total number of subjects in the interim analysis	
Subject analysis set title	All LST PPP
Subject analysis set type	Per protocol
Subject analysis set description: All subjects receiving LST tablets (OXN80/40mg and OXN60/30mg)	
Subject analysis set title	All HST PPP
Subject analysis set type	Per protocol
Subject analysis set description: All subjects receiving HST tablets (OXN80/40mg and OXN60/30mg)	

Primary: Analgesic efficacy based on the mean of subjects' 'Average Pain over the last 24 hours' at the last 2 visits of each Cross-over Period, as assessed by the Pain Intensity Scale

End point title	Analgesic efficacy based on the mean of subjects' 'Average Pain over the last 24 hours' at the last 2 visits of each Cross-over Period, as assessed by the Pain Intensity Scale
End point description: Pain Intensity Scale (Numeric Rating Scale (NRS) 0 – 10) – 'Average Pain over the last 24 hours', as assessed at Visits 5 and 6 and at Visits 8 and 9, respectively. The Primary analysis was done in the Interim Analysis. As the interim analysis already successfully proved equivalence in the average pain over the last 24 hours the analyses with the PPP and FAP were assumed to be descriptive.	
End point type	Primary
End point timeframe: 3 weeks, assessed after 2 and 3 weeks.	

End point values	OXN80/40 LST PPP	OXN80/40 HST PPP	OXN60/30 HST PPP	OXN60/30 LST PPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49[1]	49[2]	48[3]	48[4]
Units: Mean NRS over last 24 hours				
arithmetic mean (standard deviation)				
Week 2 (Visit 5 or 8)	3.49 (± 1.043)	3.61 (± 1.397)	3.02 (± 1.082)	3.31 (± 1.24)
Week 3 (Visit 6 or 9)	3.43 (± 1.118)	3.36 (± 1.253)	3.27 (± 1.106)	3.23 (± 1.077)

Notes:

[1] - Excluding subjects from the interim analysis

[2] - Excluding subjects from the interim analysis

[3] - Excluding subjects from the interim analysis

[4] - Excluding subjects from the interim analysis

End point values	Total PPP	OXN80/40 LST Interim	OXN80/40 HST Interim	OXN60/30 HST Interim
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	97[5]	20	20	20
Units: Mean NRS over last 24 hours				
arithmetic mean (standard deviation)				
Week 2 (Visit 5 or 8)	3.36 (± 1.115)	3.5 (± 1.32)	3.3 (± 1.3)	3.3 (± 0.73)
Week 3 (Visit 6 or 9)	3.39 (± 1.073)	3.5 (± 1.23)	3.5 (± 1.15)	3.4 (± 1.1)

Notes:

[5] - Excluding subjects from the interim analysis

End point values	OXN60/30 LST Interim	Interim total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	40		
Units: Mean NRS over last 24 hours				
arithmetic mean (standard deviation)				
Week 2 (Visit 5 or 8)	3.3 (± 1.21)	3.3 (± 1.06)		
Week 3 (Visit 6 or 9)	3.4 (± 1.18)	3.4 (± 1.02)		

Statistical analyses

Statistical analysis title	Equivalence Ratio OXN60/30 Interim

Statistical analysis description:

LST:HST ratio for OXN 60/30 dose interim analysis

Comparison groups	OXN60/30 HST Interim v OXN60/30 LST Interim

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence[6]
Parameter estimate	Ratio (LST:HST)
Point estimate	1.02
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	0.88
upper limit	1.17

Notes:

[6] - The average pain over the past 24 hours over the last 2 weeks of each period were analysed following the approach described in Hauschke et al., 1999 for proving equivalence based on the ratio of 2 mean values from a cross-over design. The analysis concluded on equivalence of tested treatments if the two-sided (1-α)% Fieller confidence interval for the ratio of the mean treatment effects (HST/LST) over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

Statistical analysis title	Equivalence Ratio OXN80/40 Interim

Statistical analysis description:

LST:HST ratio for OXN 80/40 dose interim analysis (20 subjects)

Comparison groups	OXN80/40 LST Interim v OXN80/40 HST Interim
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence[7]
Parameter estimate	Ratio (LST:HST)
Point estimate	0.97
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	0.86
upper limit	1.09

Notes:

[7] - The average pain over the past 24 hours over the last 2 weeks of each period were analysed following the approach described in Hauschke et al., 1999 for proving equivalence based on the ratio of 2 mean values from a cross-over design. The analysis concluded on equivalence of tested treatments if the two-sided (1-α)% Fieller confidence interval for the ratio of the mean treatment effects (HST/LST) over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

Statistical analysis title	Equivalence Ratio OXN60/30 PPP

Statistical analysis description:

LST:HST ratio for OXN 60/30 dose Per Protocol Population (48 subjects)

Comparison groups	OXN60/30 LST PPP v OXN60/30 HST PPP
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	equivalence[8]
Parameter estimate	Ratio (LST:HST)
Point estimate	0.96
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	0.9
upper limit	1.03

Notes:

[8] - The average pain over the past 24 hours over the last 2 weeks of each period were analysed following the approach described in Hauschke et al., 1999 for proving equivalence based on the ratio of 2 mean values from a cross-over design. The analysis concluded on equivalence of tested treatments if the two-sided (1-α)% Fieller confidence interval for the ratio of the mean treatment effects (HST/LST) over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

Statistical analysis title	Equivalence Ratio OXN80/40 PPP

Statistical analysis description:

LST:HST ratio for OXN 80/40 dose Per Protocol Population (49 subjects)

Comparison groups	OXN80/40 HST PPP v OXN80/40 LST PPP
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	equivalence[9]
Parameter estimate	Ratio (LST:HST)
Point estimate	1.05
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	0.97
upper limit	1.13

Notes:

[9] - The average pain over the past 24 hours over the last 2 weeks of each period were analysed following the approach described in Hauschke et al., 1999 for proving equivalence based on the ratio of 2 mean values from a cross-over design. The analysis concluded on equivalence of tested treatments if the two-sided (1-α)% Fieller confidence interval for the ratio of the mean treatment effects (HST/LST) over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

Primary: Equivalence of bowel function between LST an HST treatment

End point title	Equivalence of bowel function between LST an HST treatment

End point description:

BFI, as assessed at Visits 5 and 6 and at Visits 8 and 9, respectively. The BFI was the mean of the following items: Ease of defecation (NAS, 0=easy/no difficulty; 100=severe difficulty), Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100=very strong), Personal judgement of constipation (NAS, 0=not at all, 100=very strong).

End point type	Primary

End point timeframe:

3 weeks, assessed after 2 and 3 weeks.

End point values	OXN80/40 LST PPP	OXN80/40 HST PPP	OXN60/30 HST PPP	OXN60/30 LST PPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	68	68
Units: Bowel Function Index (BFI)				
arithmetic mean (standard deviation)				
Week 2 (Visit 5 or 8)	23.191 (± 23.2139)	23.039 (± 24.0914)	25.662 (± 23.6688)	23.971 (± 22.503)
Week 3 (Visit 6 or 9)	25.206 (± 26.0478)	23.73 (± 22.5886)	23.172 (± 19.6078)	20.466 (± 21.1836)

End point values	Total PPP	All LST PPP	All HST PPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	136	136	136	
Units: Bowel Function Index (BFI)				
arithmetic mean (standard deviation)				
Week 2 (Visit 5 or 8)	23.966 (± 22.4976)	23.581 (± 22.7798)	24.35 (± 23.8288)	
Week 3 (Visit 6 or 9)	23.143 (± 21.4904)	22.836 (± 23.7718)	23.451 (± 21.0741)	

Statistical analyses

Statistical analysis title	BFI LST:HST ratio 60/30mg treatment

Statistical analysis description:

LST:HST ratio of BFI for subjects in the OXN 60/30mg dose group (68 subjects)

Comparison groups	OXN60/30 LST PPP v OXN60/30 HST PPP
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[10]
Parameter estimate	Ratio (LST:HST)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.24

Notes:

[10] - The co-primary efficacy analysis on the BFI applied the procedure described in Hauschke et al., 1999 for proving equivalence based on the ratio of two mean values from a cross-over design concluding on equivalence of tested treatments if the two-sided (1-α)% Fieller confidence interval for the expected ratio of the mean treatment effects over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

Statistical analysis title	BFI LST:HST ratio 80/40mg treatment

Statistical analysis description:

LST:HST ratio of BFI for subjects in the OXN 80/40mg dose group (68 subjects)

Comparison groups	OXN80/40 LST PPP v OXN80/40 HST PPP
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[11]
Parameter estimate	Ratio (LST:HST)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.06

Notes:

[11] - The co-primary efficacy analysis on the BFI applied the procedure described in Hauschke et al., 1999 for proving equivalence based on the ratio of two mean values from a cross-over design concluding on equivalence of tested treatments if the two-sided (1-α)% Fieller confidence interval for the expected ratio of the mean treatment effects over the last 2 weeks of each period was fully

contained in an equivalence range of 80% to 125%.

Statistical analysis title	BFI LST:HST ratio all subjects in the PPP
Statistical analysis description:	
LST:HST ratio of BFI for all subjects in the Per Protocol Population (136 subjects)	
Comparison groups	All LST PPP v All HST PPP
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	equivalence[12]
Parameter estimate	Ratio (LST:HST)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.11

Notes:

[12] - The co-primary efficacy analysis on the BFI applied the procedure described in Hauschke et al., 1999 for proving equivalence based on the ratio of two mean values from a cross-over design concluding on equivalence of tested treatments if the two-sided (1-α)% Fieller confidence interval for the expected ratio of the mean treatment effects over the last 2 weeks of each period was fully contained in an equivalence range of 80% to 125%.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Events were recorded from the point at which the Informed Consent was signed until 7 days after the subject left the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	OXN80/40 PR LST

Reporting group description:

Subjects who received OXN Low Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

Reporting group title	OXN80/40 PR HST

Reporting group description:

Subjects who received OXN High Strength Tablet on a dose level of 80 mg oxycodone and 40 mg naloxone.

Reporting group title	OXN60/30 PR LST

Reporting group description:

Subjects who received OXN Low Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

Reporting group title	OXN60/30 PR HST

Reporting group description:

Subjects who received OXN High Strength Tablet on a dose level of 60 mg oxycodone and 30 mg naloxone.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No single adverse event occurred at a freqency of 5% or more. In the Double-blind Phase, 60 (38.8%) subjects experienced 137 AEs, of which 26 in 16 (10.4%) subjects were related to IMP.
Subjects with AEs per treatment group:
OXN60/30 PR LST (N=75): 14
OXN60/30 PR HST (N=73): 15
OXN80/40 PR LST (N=79): 25
OXN80/40 PR HST (N=76): 18

Serious adverse events	OXN80/40 PR LST	OXN80/40 PR HST	OXN60/30 PR LST
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 79 (2.53%)	1 / 76 (1.32%)	1 / 75 (1.33%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm	Additional description: Not related to IMP		
subjects affected / exposed	0 / 79 (0.00%)	0 / 76 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression	Additional description: All occurrences unrelated to IMP		

subjects affected / exposed	2 / 79 (2.53%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Nervous system disorders			
Petit mal epilepsy	Additional description: Not related to IMP		
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	0 / 75 (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
Blood and lymphatic system disorders			
Anaemia	Additional description: Not related to IMP		
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	0 / 75 (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

Serious adverse events	OXN60/30 PR HST		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 73 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm	Additional description: Not related to IMP		
subjects affected / exposed	0 / 73 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression	Additional description: All occurrences unrelated to IMP		
subjects affected / exposed	0 / 73 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Petit mal epilepsy	Additional description: Not related to IMP		
subjects affected / exposed	0 / 73 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia	Additional description: Not related to IMP		

subjects affected / exposed	0 / 73 (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	OXN80/40 PR LST	OXN80/40 PR HST	OXN60/30 PR LST
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 79 (0.00%)	0 / 76 (0.00%)	0 / 75 (0.00%)

Non-serious adverse events	OXN60/30 PR HST		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 73 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2014	This Substantial Protocol Amendment added the Pain Intensity Scale – 'Pain right now' in the diaries of the Double-blind Phase, and as a further secondary objective of this study. The objective was phrased • To assess analgesic efficacy at intake of oxycodone/naloxone tablets during the last 2 weeks of each Cross-over Period. Table 1 and its footnotes were changed to include the 'Pain right now' documentation in the diary.
11 December 2014	This Non-Substantial Protocol Amendment recalculated the CV as requested by the Research Ethics Committee (UK) regarding pain based on clinical study OXN3506 and BFI based on clinical study OXN3401, and adjusted the sample size in accordance therewith. In the sample size estimation for the number of subjects to be analysed for 'Average pain over the last 24 hours' the CV between subjects changed from 0.29 to 0.27 and the CV within subjects from 0.29 to 0.15 for the arithmetic average of 2 visits. This changed the required number of evaluable subjects per OXN dose level from 24 subjects to 26 subjects, the total number of subjects from 48 to 52 and the number of subjects in the interim analysis from 36 to 40. For BFI, the CV was recalculated, resulting in a change of CV within subjects from 0.72 to 0.38 for the arithmetic average of 2 visits, and in number of evaluable subjects required to provide a power of ≥ 88% from 84 to 92. Overall the number of subjects to be randomised changed from 132 to 144.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported