Clinical trial results:
An exploratory, double-blind, double-dummy, randomised, 2-period, crossover, Phase IIa study to assess the influence of oxycodone/naloxone prolonged-release tablets (OXN PR) and oxycodone prolonged-release tablets (OxyPR) on intestinal microbiota and other gastrointestinal parameters in subjects suffering from non-malignant pain requiring an equivalent of 20 – 50 mg oxycodone prolonged-release per day

Summary

EudraCT number	2012-001772-11
Trial protocol	CZ
Global end of trial date	09 February 2015

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	OXN2505

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research GmbH
Sponsor organisation address	Höhenstraße 10, Limburg, United Kingdom, D-65549
Public contact	Clinical Trial Contact , Mundipharma Research GmbH & Co. KG, +44 1223424900, info@contact-clinical-trial.com
Scientific contact	Clinical Trial Contact , Mundipharma Research GmbH & Co. KG, +44 1223424900, 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	09 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2015
Global end of trial reached?	Yes
Global end of trial date	09 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• Quantitative analysis of intestinal microbiota as determined in stool samples of subjects treated with OXN PR compared to those treated with OxyPR.
• To assess orocaecal transit time on the basis of intestinal absorption and intermediary bacterial metabolism as determined by breath tests (H2 breath test, CH4 breath test) in subjects treated with OXN PR compared to those treated with OxyPR.

Protection of trial subjects:

1) Inclusion criteria:
- Females less than one year post-menopausal had to have a negative 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 is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly e.g. sterilisation, implants, injectables, combined oral contraceptives, some intrauterine devices ((IUDs), 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 visits at pain and GE centres, 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 may have stopped study treatment at any time for safety or personal reasons.
Subjects with serious diarrhoea, withdrawal syndrome, vital sign or laboratory abnormalities were also to be discontinued.
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 and abuse. In addition, safety was assessed by monitoring haematology, biochemistry, and urine values, periodic measurement of vital signs and ECGs and the performance of physical examinations.

Background therapy:

Non-Investigational Medicinal Products (NIMPs) included rescue mediation as well as substances used in the breath tests.
- OxyIR use (Run-in Period and Double-Blind Phase, Opioid-treated subjects (OTS) only):
OxyIR was the only allowed rescue pain medication. It was to be dosed no sooner than every 4 hours as needed. For subjects receiving 20, 30 or 40 mg/day of oxycodone PR, the single rescue dose of OxyIR was 5 mg. For subjects receiving 50 mg/day of oxycodone PR, the single rescue dose of OxyIR was 10 mg.
- Bisacodyl (Run-in Period and Double-Blind Phase, OTS only):
As rescue medication for constipation, only bisacodyl suppository were to be used no sooner than 72 hours after a subject's most recent bowel movement.
- Mouthwash (Vademecum med® concentrate or equivalent product) (breath tests at Gastroenterological (GE) centres):
Five splatters in a half glass of tap water (appr. 0.1 Liter) were given to subjects prior to the first breath test assessment.
- Lactulose (breath tests at GE centres):
A test solution was prepared ahead of each breath test assessment, containing 10 g lactulose (15 mL solution of Bifiteral®) plus 200 mL tap water.

- Glucose and Insulin:
Both NIMPs were administered at GE centres on an “as required” basis and at the discretion of the Investigator in subjects diagnosed with diabetes mellitus.

Evidence for comparator:

Oxycodone/naloxone prolonged release (OXN), the investigational drug in this study, has comparable analgesic effficacy as oxycodone prolonged release (OxyPR), but causes less opioid-induced bowel dysfunction. This study is aimed to generate data about different gastrointestinal parameters in response to treatment of constipated subjects with OXN PR and OxyPR.

Actual start date of recruitment	22 July 2013
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	Czech Republic: 30
Country: Number of subjects enrolled	Germany: 122
Worldwide total number of subjects	152
EEA total number of subjects	152

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)	121
From 65 to 84 years	29
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 2 countries at 27 pain centres (23 sites in Germany, 4 sites in the Czech Republic) and 6 Gastrointestinal (GE) centres (5 sites in Germany, 1 site in the Czech Republic). In addition, 10 pain centres in Germany were initiated but did not recruit any subjects.

Pre-assignment

Screening details:

OTS were screened for up to 14 days, followed by a Run-in period of 7-28 days. During the Run-In Period subjects had their opioid therapy converted to open-label OxyPR, which was titrated to an effective analgesic dose between 20-50 mg of Oxy PR per day (20, 30, 40 or 50 mg per day).

Pre-assignment period milestones

Number of subjects started	152
Number of subjects completed	108[1]

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 6
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Run-in failure: 11
Reason: Number of subjects	Screening failure: 25

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: As this is a cross-over study, 54 subjects started in each Treatment Group at the beginning of the double-blind Phase. Subjects who discontinued in cross-over period 1 were not included in subject numbers for cross-over period 2.

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	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

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. Medication codes were not available until the completion of the study and until clinical data base lock, except in the case of emergency. Unblinding of treatment in single subject for regulatory reporting of SUSARs was done by designated drug safety personnel only

Arms

Are arms mutually exclusive?	No
Arm title	OXN PR

Arm description:

All subjects taking OXN PR in cross-over period 1 or cross-over period 2

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

Dosage and administration details:

OXN PR and matching placebos in the DB-Phase were blinded and administered orally, prescribed q12h. Dosing was fixed and symmetrical (20, 30, 40 or 50 mg/day of oxycodone PR).

Arm title	OxyPR

Arm description:

All subjects taking OxyPR in cross-over period 1 or cross-over period 2

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

Dosage and administration details:

OxyPR and matching placebos in the DB-Phase were blinded and administered orally, prescribed q12h. Dosing was fixed and symmetrical (20, 30, 40 or 50 mg/day of oxycodone PR).

Number of subjects in period 1	OXN PR	OxyPR
Started	104	104
Completed	100	98
Not completed	4	6
Consent withdrawn by subject	3	1
Administrative	1	2
Adverse event, non-fatal	-	3

Baseline characteristics

Reporting groups[1]

Reporting group title	Double-blind period

Reporting group description: -

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: As this is a cross-over study, 54 subjects started in each Treatment Group at the beginning of the double-blind Phase. Subjects who discontinued in cross-over period 1 were not included in subject numbers for cross-over period 2.

Reporting group values	Double-blind period	Total	
Number of subjects	108	108	
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 years and older)	108	108	
Age continuous Units: years			
arithmetic mean	57.5		
standard deviation	± 10.75	-	
Gender categorical Units: Subjects			
Female	76	76	
Male	32	32	

Subject analysis sets

Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis population is defined as all randomised subjects who receive at least one dose of IMPs and have at least one post-baseline assessments of the primary efficacy variables in each of the two treatment periods.
All subjects which are part of the FAP are regarded as evaluable. In case that many subjects have only data from one treatment period a sensitivity analysis based on the reduced population will be considered

Subject analysis set title	Double Blind Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Double-blind safety population is defined as all enrolled subjects who were randomised and received at least one dose of IMP and have at least one safety assessment in the Double-Blind Phase.

Reporting group values	Full Analysis Population	Double Blind Safety Population	
Number of subjects	98	108	

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 years and older)	98	108	
Age continuous Units: years			
arithmetic mean	56.8	57.5	
standard deviation	± 10.32	± 10.75	
Gender categorical Units: Subjects			
Female	68	76	
Male	30	32	

End points

End points reporting groups

Reporting group title	OXN PR
Reporting group description:	
All subjects taking OXN PR in cross-over period 1 or cross-over period 2	
Reporting group title	OxyPR
Reporting group description:	
All subjects taking OxyPR in cross-over period 1 or cross-over period 2	
Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis population is defined as all randomised subjects who receive at least one dose of IMPs and have at least one post-baseline assessments of the primary efficacy variables in each of the two treatment periods. All subjects which are part of the FAP are regarded as evaluable. In case that many subjects have only data from one treatment period a sensitivity analysis based on the reduced population will be considered	
Subject analysis set title	Double Blind Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Double-blind safety population is defined as all enrolled subjects who were randomised and received at least one dose of IMP and have at least one safety assessment in the Double-Blind Phase.	

Primary: Orocaecal transit time

End point title	Orocaecal transit time
End point description:	
To assess orocaecal transit time on the basis of intestinal absorption and intermediary bacterial metabolism as determined by breath tests (H2 breath test, CH4 breath test) in subjects treated with OXN PR compared to those treated with OxyPR. Orocaecal time was measured by H2/CH4/ analysis of expired air of subjects (breath tests).	
End point type	Primary
End point timeframe:	
Breath test assessments at 5 minute intervals for H2/CH4: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180 + Extension by 1 hour if needed.	

End point values	OXN PR	OxyPR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	62		
Units: Minutes				
least squares mean (confidence interval 95%)	124.58 (112.47 to 136.69)	131 (118.59 to 143.41)		

Statistical analyses

Statistical analysis title	Difference in LS Means

Statistical analysis description:

ANOVA with fixed terms for treatment, period and sequence and a random subject effect

Comparison groups	OXN PR v OxyPR
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.446
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.21
upper limit	10.37

Notes:

[1] - The H2-CH4-breath test provides the exhalation results of H2 and CH4 in the ppm unit, while the 1-13C-sodium acetate breath test measures the ratio between 12C and 13C in breath samples (given as delta‰) and calculates the DOB value (delta over basal, given as delta‰) and the percentage of the 13C-dose exhaled per hour as %13C dose/h.
Gastric emptying time is defined as the time of maximum 13C-CO2 [%13C dose/h] exhalation.
Orocaecal transit time is defined as the first timepoint where H2 [ppm]

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events were recorded from the point at which the Informed Consent is signed until 7 days after the subject left the study. This included new AEs that were reported in the 7 days following the subject's completion/discontinuation visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	OXN PR

Reporting group description:

All subjects taking OXN PR in cross-over period 1 or cross-over period 2

Reporting group title	OxyPR

Reporting group description:

All subjects taking OxyPR in cross-over period 1 or cross-over period 2

Serious adverse events	OXN PR	OxyPR	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 104 (0.96%)	1 / 104 (0.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Gastroenteritis	Additional description: assessed as not related to IMP caused hospitalisation subject recovered		
subjects affected / exposed	1 / 104 (0.96%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroneteritis salmonella	Additional description: assessed as not related to IMP caused hospitalisation subject recovered		
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
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: 4.8 %

Non-serious adverse events	OXN PR	OxyPR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 104 (9.62%)	15 / 104 (14.42%)	
Investigations			
Blood uric acid increased	Additional description: All AEs of uric acid increased were not causally related to IMP.		
subjects affected / exposed	4 / 104 (3.85%)	5 / 104 (4.81%)	
occurrences (all)	4	5	
Gastrointestinal disorders			
Diarrhoea	Additional description: 3 AEs of diarrhoea in OXN PR Group and 2 in OxyPR Group were causally unrelated to IMP		
subjects affected / exposed	5 / 104 (4.81%)	3 / 104 (2.88%)	
occurrences (all)	5	3	
Infections and infestations			
Nasopharyngitis	Additional description: all AEs of nasopharyngitis were causally unrelated to IMP.		
subjects affected / exposed	2 / 104 (1.92%)	8 / 104 (7.69%)	
occurrences (all)	2	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2013	Protocol Amendment No. 1 was a result of the German central Ethic Committee's (cEC) response to the submission of the protocol 15-NOV-2012. The cEC responded on the 30 January 2013. The amendment is considered a "substantial amendment" as sections of it affect in- and exclusion criteria. In addition, minor text corrections and inconsistencies have been corrected.
16 May 2013	Protocol Amendment No. 2 was a result of the response letter by the German competent authority (BfArM) dated 02 April 2013. The Sponsor had obtained a conditional approval for the study. The condition was to submit a manufacturing license for the weighing and filling of 13C-Sodium Acetate. Since the process to get the manufacturing license for this product would have been very complex, involving release by a qualified person and additional documentation, the Sponsor decided to remove the 13C-Sodium Acetate breath test from the study. The amendment was considered a "substantial amendment" because of changes to study procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported