Clinical trial results:
Randomised, double-blind, placebo-controlled, parallel-group design, multi-centre, dose-escalation phase III trial to investigate the efficacy, safety, and tolerability of Naloxone HCl PR tablets administered in a dose range of 3 mg to 24 mg twice daily in patients with opioid induced constipation

Summary

EudraCT number	2012-003218-14
Trial protocol	DE HU CZ SK ES IT
Global end of trial date	19 August 2014

Results information

Result version number	v1 (current)
This version publication date	15 May 2020
First version publication date	15 May 2020
Summary attachment (see zip file)	0176/DEV (0176DEV CSR synopsis_Synopsis extracted.pdf)

Trial information

Trial identification

Sponsor protocol code	0176/DEV

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Develco Pharma Schweiz AG
Sponsor organisation address	Hohenrainstr. 12 D, Pratteln, Switzerland, 4133
Public contact	Head Clinical Development, Develco Pharma Schweiz AG, 0041 614255026, info@develco.ch
Scientific contact	Head Clinical Development, Develco Pharma Schweiz AG, 0041 614255026, info@develco.ch

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	19 August 2014
Global end of trial reached?	Yes
Global end of trial date	19 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that administration of Naloxone HCl PR (prolonged-release) tablets twice daily is superior to Naloxone HCl PR Placebo in the improvement / reversal of opioid-induced constipation (OIC) as determined by the Bowel Function Index (BFI)

Protection of trial subjects:

The trial was conducted in compliance with the protocol, by trial personnel, who are qualified by education, training, and experience in their roles, with adherence to Good Clinical Practice (GCP), the applicable regulatory requirements and ethical principles based on the Declaration of Helsinki.

Background therapy:

Opioid rescue medication:
•Morphine sulphate 10 mg immediate-release tablets, oral administration, as needed, single dose: 5-20 mg, depending on trial opioid dose
Laxative rescue medications:
•Bisacodyl 5 mg gastro-resistant tablets, oral administration, single dose: 5-20 mg (1-4 tablets)
•Bisacodyl 10 mg suppositories, rectal administration, single dose: 10 mg, 1 suppository

Evidence for comparator: -

Actual start date of recruitment	12 March 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: 35
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Hungary: 72
Country: Number of subjects enrolled	Slovakia: 16
Worldwide total number of subjects	173
EEA total number of subjects	173

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	51
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects of ≥ 18 years of age with documented history of constipation induced or worsened by their oral or sublingual World Health Organization (WHO) step-II or step-III opioid medication were recruited.

Pre-assignment

Screening details:

A total of 298 subjects were screened, out of these, 173 subjects were randomized. 64 subjects were screening failures. Further 61 screened subjects prematurely discontinued from the trial before randomisation.

Pre-assignment period milestones

Number of subjects started	298[1]
Number of subjects completed	173

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 18
Reason: Number of subjects	Adverse event, serious non-fatal: 2
Reason: Number of subjects	Consent withdrawn by subject: 22
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Noneligibility: 61
Reason: Number of subjects	Other: 21

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number enrolled subjects in the trial is the number of randomized subjects.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Overall - NLX

Arm description:

Subjects received Naloxone (NLX) hydrochloride (HCl) prolonged-release (PR) tablets (3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, total daily dose: 6-48 mg

Arm type	Experimental
Investigational medicinal product name	Naloxone hydrochloride
Investigational medicinal product code	NLX
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Total daily dose: 6-48 mg
Subjects will start with the lowest total daily dose of 6 mg IMP and will be treated on this dose level for 2 weeks. After 2 weeks, the dose will be escalated to 12 mg IMP per day for a further 2 weeks. Each further escalation step (dose level of 24 mg and 48 mg IMP per day) will last for at least 2 weeks.

Arm title	Overall - Placebo

Arm description:

Subjects receive corresponding placebo tablets (1.5 mg, 3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, total daily dose: 3-48 mg

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

Dosage and administration details:

Total daily dose: 6-48 mg
All subjects will be treated with NLX PLA 1.5 mg during Run-in.
In Treatment phase subjects will start with the lowest total daily dose of 6 mg IMP and will be treated on this dose level for 2 weeks. After 2 weeks, the dose will be escalated to 12 mg IMP per day for a further 2 weeks. Each further escalation step (dose level of 24 mg and 48 mg IMP per day) will last for at least 2 weeks.

Number of subjects in period 1	Overall - NLX	Overall - Placebo
Started	115	58
Completed	97	50
Not completed	18	8
Consent withdrawn by subject	4	-
Treatment failure	7	3
Adverse event, non-fatal	4	2
Other	1	-
Adverse event, serious non-fatal	1	1
Noneligibility	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall - NLX
Reporting group description:	
Subjects received Naloxone (NLX) hydrochloride (HCl) prolonged-release (PR) tablets (3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, total daily dose: 6-48 mg	
Reporting group title	Overall - Placebo
Reporting group description:	
Subjects receive corresponding placebo tablets (1.5 mg, 3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, total daily dose: 3-48 mg	

Reporting group values	Overall - NLX	Overall - Placebo	Total
Number of subjects	115	58	173
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0
Newborns (0-27days)	0	0	0
Infants and toddlers (28days – 23months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 year)	0	0	0
From 18 - 64 years	74	47	121
From 65 – 84 years	40	11	51
Over 85 years	1	0	1
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	59	55.56	
standard deviation	± 12.19	± 9.92	-
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	76	40	116
Male	39	18	57

End points

End points reporting groups

Reporting group title	Overall - NLX
Reporting group description:	
Subjects received Naloxone (NLX) hydrochloride (HCl) prolonged-release (PR) tablets (3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, total daily dose: 6-48 mg	
Reporting group title	Overall - Placebo
Reporting group description:	
Subjects receive corresponding placebo tablets (1.5 mg, 3 mg, 6 mg, 12 mg, 24 mg), oral administration, twice daily, total daily dose: 3-48 mg	
Subject analysis set title	Overall - NLX x Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised subjects who received at least one dose of the double-blind trial medication.	
Subject analysis set title	Overall - Placebo x Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised subjects who received at least one dose of the double-blind trial medication.	
Subject analysis set title	Overall - NLX x FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised subjects, who receive at least one dose of the double-blind trial medication, and with at least one post-baseline (i.e. after Visit 4) assessment of BFI during the double-blind dose-escalation/treatment phase.	
Subject analysis set title	Overall - Placebo x FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised subjects, who receive at least one dose of the double-blind trial medication, and with at least one post-baseline (i.e. after Visit 4) assessment of BFI during the double-blind dose-escalation/treatment phase.	

Primary: BFI absolute change

End point title	BFI absolute change
End point description:	
BFI absolute change between baseline (Visit 4) and the end of Week 12 of the double-blind dose-escalation / treatment phase	
End point type	Primary
End point timeframe:	
Baseline up to Week 12 in Treatment Phase	

End point values	Overall - NLX x FAS	Overall - Placebo x FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	114	58		
Units: BFI score				
number (standard deviation)				
BFI score	114	58		

Statistical analyses

Statistical analysis title	Statistical Analysis of BFI - LOCF

Statistical analysis description:

ANCOVA is carried out using treatment, centre, age (≤65 years; >65 years), sex, opioid drug (oxycodone or hydromorphone) and opioid TDD (low-dose range; high-dose range) as categorical factors, and baseline BFI and number of days with laxative rescue medication use during the last 4 weeks as continuous covariates

Comparison groups	Overall - NLX x FAS v Overall - Placebo x FAS
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0478
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-6.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.23
upper limit	-0.06

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first intake of IMP and not more than 14 days after last administration of IMP	
Adverse event reporting additional description:	
Numbers of TEAEs are reported.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Overall - Placebo x Safety
Reporting group description:	
Subjects in the Safety set treated with Placebo	
Reporting group title	Overall - NLX x Safety
Reporting group description:	
Subjects in the Safety set treated with NLX	

Serious adverse events	Overall - Placebo x Safety	Overall - NLX x Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 58 (1.72%)	3 / 115 (2.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular injury			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Post-traumatic stress disorder			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
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: 0 %

Non-serious adverse events	Overall - Placebo x Safety	Overall - NLX x Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 58 (46.55%)	71 / 115 (61.74%)	
Vascular disorders			
Hot flush			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	1 / 115 (0.87%)	
occurrences (all)	1	2	
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	3 / 115 (2.61%)	
occurrences (all)	0	3	
Hypertensive crisis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Hypotension			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Lymphoedema			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Phlebitis superficial			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Vascular calcification			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Tooth extraction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Drug withdrawal syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Pain			
alternative assessment type:			

Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Spinal pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	2	
Immune system disorders			
Hypersensitivity			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Bronchopneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Cystitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	2	0	
Fungal infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Gastritis viral			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Herpes zoster			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Infected bites			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Influenza			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	2 / 115 (1.74%)	
occurrences (all)	1	2	
Laryngitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 58 (8.62%)	12 / 115 (10.43%)	
occurrences (all)	5	15	
Oral herpes			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	

Otitis media			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Periodontitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Pharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	2 / 115 (1.74%)	
occurrences (all)	0	2	
Pulpitis dental			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Rhinitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	3 / 115 (2.61%)	
occurrences (all)	0	3	
Tonsillitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Viral diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Viral infection			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 58 (1.72%)	2 / 115 (1.74%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
Menopausal symptoms			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Metrorrhagia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Dysphonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Oropharyngeal pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	3 / 115 (2.61%)	
occurrences (all)	0	3	
Rhinorrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 58 (5.17%)	1 / 115 (0.87%)	
occurrences (all)	3	1	
Psychiatric disorders			
Anxiety disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Nervousness			
alternative assessment type:			

Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Psychotic disorder due to a general medical condition			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Restlessness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Tension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	2	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Blood glucose increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	2 / 115 (1.74%)	
occurrences (all)	0	2	
Body temperature increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Weight decreased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Burn oesophageal			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Concussion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Face injury			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Hand fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Jaw fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Ligament rupture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Rib fracture			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Wrist fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Dilatation ventricular			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 58 (5.17%)	2 / 115 (1.74%)	
occurrences (all)	3	2	
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 58 (13.79%)	15 / 115 (13.04%)	
occurrences (all)	10	19	
Hypoaesthesia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 58 (0.00%)	2 / 115 (1.74%)	
occurrences (all)	0	2	
Tinnitus			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	2 / 115 (1.74%)	
occurrences (all)	1	2	
Eye disorders			
Lacrimation increased			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 58 (5.17%)	1 / 115 (0.87%)	
occurrences (all)	3	1	
Photophobia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	1 / 115 (0.87%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	2 / 115 (1.74%)	
occurrences (all)	1	2	
Abdominal distension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	4 / 115 (3.48%)	
occurrences (all)	1	4	
Abdominal pain			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 58 (5.17%)	4 / 115 (3.48%)	
occurrences (all)	4	4	
Abdominal pain upper			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	1 / 115 (0.87%)	
occurrences (all)	1	1	
Anorectal discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Defaecation urgency			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	9 / 115 (7.83%)	
occurrences (all)	0	15	
Dyspepsia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	2 / 115 (1.74%)	
occurrences (all)	0	2	
Frequent bowel movements			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Gastritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	

Gastrointestinal hypomotility			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 58 (5.17%)	6 / 115 (5.22%)	
occurrences (all)	3	6	
Salivary hypersecretion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Toothache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	1 / 115 (0.87%)	
occurrences (all)	1	1	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	2 / 115 (1.74%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Erythema			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Hyperhidrosis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 58 (1.72%)	3 / 115 (2.61%)	
occurrences (all)	1	4	
Nail disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Rash			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 58 (3.45%)	6 / 115 (5.22%)	
occurrences (all)	2	6	
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 58 (3.45%)	5 / 115 (4.35%)	
occurrences (all)	2	5	
Flank pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Joint swelling			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Limb deformity			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Musculoskeletal pain			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 58 (0.00%)	3 / 115 (2.61%)	
occurrences (all)	0	3	
Pain in extremity			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	3 / 115 (2.61%)	
occurrences (all)	1	3	
Spinal osteoarthritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Tendinous contracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Hyperglycaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Increased appetite			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	
occurrences (all)	1	0	
Type 2 diabetes mellitus			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2013	Global Protocol Amendment No. 2 It broadens exclusion criterion no. 9 due to revised safety considerations justified by existing literature and SmPCs of drugs containing naloxone hydrochloride PR.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported