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 6 mg to 48 mg once daily in patients with opioid induced constipation

Summary

EudraCT number	2012-004311-31
Trial protocol	HU AT CZ DE GB SK ES IT PL
Global end of trial date	01 December 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)	0177/DEV (0177-DEV_CSR_Final version 1.0_16JUN2015_clean_Synopsis extracted.pdf)

Trial information

Trial identification

Sponsor protocol code	0177/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	09 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2014
Global end of trial reached?	Yes
Global end of trial date	01 December 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 once 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 will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996), as well as with the valid national law(s) of the participating country/ies, with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (E6) issued in June 1996, and with the Commission Directives 2001/20/EC and 2005/28/EC.

Background therapy:

Trial opioids:
Oxycodone (Oxy) hydrochloride prolonged-release tablets XL (20 mg, 40 mg, 80 mg), oral administration, once daily, total daily dose: 20 mg, 40 mg, 60 mg or 80 mg
Hydromorphone (HyMo) hydrochloride prolonged-release tablets XL, (8 mg, 16 mg, 32 mg), oral administration, once daily, total daily dose: 8 mg, 16 mg, 24 mg or 32 mg
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	24 June 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: 39
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Hungary: 65
Country: Number of subjects enrolled	Slovakia: 22
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Austria: 1

Worldwide total number of subjects	183
EEA total number of subjects	183

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)	119
From 65 to 84 years	63
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

A total of 267 subjects were screened, out of these, 183 subjects were randomized. 39 subjects were screening failures. Further 45 screened subjects prematurely discontinued from the trial before randomisation.

Pre-assignment period milestones

Number of subjects started	267[1]
Number of subjects completed	183

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 19
Reason: Number of subjects	Adverse event, serious non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 5
Reason: Number of subjects	Noneligibility: 48
Reason: Number of subjects	Other: 11

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 HCl PR tablets (NLX 6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, TDD: 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:

Subjects started with the lowest total daily dose of 6 mg IMP and were treated on this dose level for 2 weeks. After 2 weeks, the dose was 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) lasted for at least 2 weeks.

Arm title	Overall - Placebo

Arm description:

Subjects receive corresponding placebo tablets (NLX PLA 3 mg [placebo run-in only], 6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, TDD: 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:

All subjects received Naloxone HCl 3 mg PR Placebo once daily for 2 weeks during run-in phase.
In Treatment phase Subjects started with the lowest total daily dose of 6 mg IMP and were treated on this dose level for 2 weeks. After 2 weeks, the dose was 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) lasted for at least 2 weeks.

Number of subjects in period 1	Overall - NLX	Overall - Placebo
Started	121	62
Completed	102	56
Not completed	19	6
Consent withdrawn by subject	1	-
Treatment failure	4	2
Adverse event, non-fatal	4	2
Other	9	2
Noneligibility	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall - NLX
Reporting group description:	
Subjects received Naloxone HCl PR tablets (NLX 6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, TDD: 6-48 mg	

Reporting group title	Overall - Placebo
Reporting group description:	
Subjects receive corresponding placebo tablets (NLX PLA 3 mg [placebo run-in only], 6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, TDD: 3-48 mg	

Reporting group values	Overall - NLX	Overall - Placebo	Total
Number of subjects	121	62	183
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	82	37	119
From 65 – 84 years	39	24	63
Over 85 years	0	1	1
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	59	60.6	
standard deviation	± 10.42	± 12.67	-
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	80	41	121
Male	41	21	62

End points

End points reporting groups

Reporting group title	Overall - NLX
Reporting group description:	
Subjects received Naloxone HCl PR tablets (NLX 6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, TDD: 6-48 mg	

Reporting group title	Overall - Placebo
Reporting group description:	
Subjects receive corresponding placebo tablets (NLX PLA 3 mg [placebo run-in only], 6 mg, 12 mg, 24 mg, 48 mg), oral administration, once daily, TDD: 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 IMP.	
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 IMP.	
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 IMP, and with at least one post-baseline (i.e. after Visit 4) assessment of BFI during the double-blind dose-escalation / treatment phase and have at least 7 days duration of 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 IMP, and with at least one post-baseline (i.e. after Visit 4) assessment of BFI during the double-blind dose-escalation / treatment phase and have at least 7 days duration of 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	121	62		
Units: BFI score				
number (standard deviation)				
BFI score	102	57		

Statistical analyses

Statistical analysis title	Statistical Analysis of BFI Score by Week
Statistical analysis description:	
BFI scores are analysed via a mixed model for repeated measures analysis, with treatment, week, pooled centre, gender, opioid and opioid TDD (low-dose, high-dose) as fixed factors, baseline BFI and standardised laxative rescue medication use per week during run-in phase as covariates	
Comparison groups	Overall - NLX x FAS v Overall - Placebo x FAS
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1534
Method	Mixed models analysis
Parameter estimate	LS Means Difference
Point estimate	-4.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.82
upper limit	1.87

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:	
Only numbers of TEAEs are reported.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

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

Serious adverse events	Overall - NLX x Safety	Overall - Placebo x Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 121 (4.13%)	0 / 62 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Cardiac failure acute			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall - NLX x Safety	Overall - Placebo x Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 121 (59.50%)	37 / 62 (59.68%)	
Vascular disorders			
Haematoma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Nerve block			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Asthenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Drug withdrawal syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	2	
Oedema peripheral			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 121 (3.31%)	2 / 62 (3.23%)	
occurrences (all)	5	2	
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Sarcoidosis			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Oropharyngeal pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Mood altered			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Nightmare			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Restlessness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Sleep disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Investigations			
Arthroscopy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
General physical condition abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Liver function test abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Weight increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Hand fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Patella fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Arrhythmia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Cardiac failure acute			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	2 / 62 (3.23%)	
occurrences (all)	3	2	
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 121 (11.57%)	9 / 62 (14.52%)	
occurrences (all)	20	12	
Hypoaesthesia			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Paraesthesia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	2 / 62 (3.23%)	
occurrences (all)	1	2	
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 121 (2.48%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Normochromic normocytic anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Thrombocytosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Lacrimation increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
alternative assessment type: Systematic			

subjects affected / exposed	11 / 121 (9.09%)	5 / 62 (8.06%)	
occurrences (all)	11	5	
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 121 (8.26%)	4 / 62 (6.45%)	
occurrences (all)	11	6	
Abdominal pain upper			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 121 (3.31%)	2 / 62 (3.23%)	
occurrences (all)	4	2	
Anal fissure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 121 (2.48%)	2 / 62 (3.23%)	
occurrences (all)	4	3	
Dry mouth			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Dyspepsia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Flatulence			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 121 (2.48%)	0 / 62 (0.00%)	
occurrences (all)	3	0	

Gastrooesophageal reflux disease			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 121 (5.79%)	5 / 62 (8.06%)	
occurrences (all)	8	6	
Toothache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	2 / 62 (3.23%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Psoriasis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Micturition disorder			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Arthritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 121 (2.48%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Bursitis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Intervertebral disc protrusion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Joint swelling			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Pain in extremity			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 121 (1.65%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Rotator cuff syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Spinal deformity			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Tendonitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Acute sinusitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	3 / 62 (4.84%)	
occurrences (all)	1	3	
Cystitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	2	
Gastroenteritis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Gastrointestinal infection			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal viral infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Influenza			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	2	
Laryngitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 121 (5.79%)	4 / 62 (6.45%)	
occurrences (all)	9	5	
Parotitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	2 / 62 (3.23%)	
occurrences (all)	2	2	

Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Viral infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 121 (1.65%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Hypercholesterolaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 121 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Hyperkalaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Increased appetite			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 62 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2013	Global Protocol Amendment No. 1 It broadens exclusion criterion no. 9 due to revised safety considerations justified by existing literature and SmPCs of drugs containing naloxone hydrochloride PR. In addition, the procedure for re-testing of laboratory tests of Visit 1 is stated more clearly. An error in Section 10.3.1 regarding trial opioid assignment is corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported