Clinical trial results:
Randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase III trial to investigate the efficacy, safety and tolerability of Naloxone HCl PR Tablets in patients with opioid induced constipation.

Summary

EudraCT number	2017-000657-39
Trial protocol	DE CZ SK ES BG PT GB HU
Global end of trial date	02 May 2019

Results information

Result version number	v1 (current)
This version publication date	20 May 2020
First version publication date	20 May 2020
Summary attachment (see zip file)	CTR Synopsis (0217DEV_CTR synopsis_Final1.0_26MAR2020.pdf)

Trial information

Trial identification

Sponsor protocol code	0217/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	Sponsor Clinical Team, Develco Pharma Schweiz AG, +41 614255020, info@develco.ch
Scientific contact	Sponsor Clinical Team, Develco Pharma Schweiz AG, +41 614255020, 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	14 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 May 2019
Global end of trial reached?	Yes
Global end of trial date	02 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Naloxone HCl PR Tablets administered twice daily at TDD of 24 mg and 48 mg over placebo in the treatment of opioid induced constipation (OIC) in terms of overall complete spontaneous bowel movement (CSBM) responder rates

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:

Laxative rescue medication: Bisacodyl 5 mg gastro-resistant tablets, oral administration, single dose: 1-4 tablets (5-20 mg).

Evidence for comparator: -

Actual start date of recruitment	31 July 2017
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	Poland: 112
Country: Number of subjects enrolled	Portugal: 22
Country: Number of subjects enrolled	Slovakia: 49
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United Kingdom: 149
Country: Number of subjects enrolled	Bulgaria: 75
Country: Number of subjects enrolled	Czech Republic: 59
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Serbia: 22
Worldwide total number of subjects	563
EEA total number of subjects	541

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	403
From 65 to 84 years	153
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Subjects of ≥ 18 years of age with opioid induced constipation

Pre-assignment

Screening details:

A total of 897 subjects were screened, out of these, 563 subjects were randomized. 75 and 259 subjects were screening and confirmation failures respectively.

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	NLX 48

Arm description:

Subjects receive Naloxone HCl PR tablets blinded using double-dummy technique, total daily dose 48 mg, oral administration, twice daily.

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

Dosage and administration details:

All patients will take two tablets of the trial medication in the morning and two tablets of the trial medication in the evening, i.e. at each intake • Naloxone HCl 24 mg PR Tablet plus Naloxone HCl 12 mg PR Placebo Tablet

Arm title	NLX 24

Arm description:

Subjects receive Naloxone HCl PR tablets blinded using double-dummy technique, total daily dose 24 mg, oral administration, twice daily

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

Dosage and administration details:

All patients will take two tablets of the trial medication in the morning and two tablets of the trial medication in the evening, i.e. at each intake • Naloxone HCl 12 mg PR Tablet plus Naloxone HCl 24 mg PR Placebo Tablet

Arm title	Placebo

Arm description:

Subjects receive corresponding placebo tablets, total daily dose: 24 or 48 mg, oral administration, twice daily

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 patients will take two tablets of the trial medication in the morning and two tablets of the trial medication in the evening, i.e. at each intake •Naloxone HCl 24 mg PR Placebo Tablet plus Naloxone HCl 12 mg PR Placebo Tablet.

Number of subjects in period 1	NLX 48	NLX 24	Placebo
Started	190	187	186
Completed	165	164	167
Not completed	25	23	19
Consent withdrawn by subject	3	2	3
Physician decision	-	-	1
Adverse event, non-fatal	20	18	10
Other	1	1	2
Lost to follow-up	-	1	-
Lack of efficacy	1	1	3

Baseline characteristics

Reporting groups	
Reporting group title	NLX 48
Reporting group description:	
Subjects receive Naloxone HCl PR tablets blinded using double-dummy technique, total daily dose 48 mg, oral administration, twice daily.	
Reporting group title	NLX 24
Reporting group description:	
Subjects receive Naloxone HCl PR tablets blinded using double-dummy technique, total daily dose 24 mg, oral administration, twice daily	
Reporting group title	Placebo
Reporting group description:	
Subjects receive corresponding placebo tablets, total daily dose: 24 or 48 mg, oral administration, twice daily	

Reporting group values	NLX 48	NLX 24	Placebo
Number of subjects	190	187	186
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	142	126	135
85 years and over	45	60	48
From 18 - 64 years	3	1	3
Age continuous Units: years			
arithmetic mean	54.7	58.4	57.1
standard deviation	± 11.55	± 11.88	± 12.17
Gender categorical Units: Subjects			
Female	117	116	116
Male	73	71	70

Reporting group values	Total		
Number of subjects	563		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	403		
85 years and over	153		
From 18 - 64 years	7		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	349		
Male	214		

End points

End points reporting groups

Reporting group title	NLX 48
Reporting group description:	
Subjects receive Naloxone HCl PR tablets blinded using double-dummy technique, total daily dose 48 mg, oral administration, twice daily.	
Reporting group title	NLX 24
Reporting group description:	
Subjects receive Naloxone HCl PR tablets blinded using double-dummy technique, total daily dose 24 mg, oral administration, twice daily	
Reporting group title	Placebo
Reporting group description:	
Subjects receive corresponding placebo tablets, total daily dose: 24 or 48 mg, oral administration, twice daily	
Subject analysis set title	NLX 48 Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised patients who received at least one dose of the double-blind trial medication.	
Subject analysis set title	NLX 24 Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised patients who received at least one dose of the double-blind trial medication.	
Subject analysis set title	Placebo Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised patients who received at least one dose of the double-blind trial medication.	
Subject analysis set title	NLX 48 FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised patients	
Subject analysis set title	NLX 24 FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised patients	
Subject analysis set title	Placebo FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised patients	

Primary: Overall CSBM response rate

End point title	Overall CSBM response rate
End point description:	
Overall CSBM response rate of Weeks 1 to 12 of Naloxone HCl 24 mg PR Tablets twice daily vs placebo and Naloxone HCl 12 mg PR Tablets twice daily vs placebo will be compared.	
End point type	Primary
End point timeframe:	
Week 1 up to Week 12	

End point values	NLX 48 FAS	NLX 24 FAS	Placebo FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	190	187	186	
Units: subjects	29	25	19	

Statistical analyses

Statistical analysis title	Overall CSBM response rate NLX 48 vs Placebo
Statistical analysis description: Statistical Analysis of Overall CSBM response rate	
Comparison groups	NLX 48 FAS v Placebo FAS
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1648
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	2.89

Statistical analysis title	Overall CSBM response rate NLX 24 vs Placebo
Statistical analysis description: Statistical Analysis of Overall CSBM response rate	
Comparison groups	NLX 24 FAS v Placebo FAS
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3725
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	2.53

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	20.0

Reporting groups	
Reporting group title	NLX 48 Safety
Reporting group description: -	
Reporting group title	NLX 24 Safety
Reporting group description: -	
Reporting group title	Placebo Safety
Reporting group description: -	

Serious adverse events	NLX 48 Safety	NLX 24 Safety	Placebo Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 191 (4.19%)	3 / 186 (1.61%)	6 / 185 (3.24%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 191 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	0 / 191 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastritis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Intestinal infarction			
subjects affected / exposed	0 / 191 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Dyspnoea			
subjects affected / exposed	0 / 191 (0.00%)	1 / 186 (0.54%)	0 / 185 (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
Dyspnoea exertional			
subjects affected / exposed	0 / 191 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Suicidal ideation			
subjects affected / exposed	0 / 191 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Chondrocalcinosis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Vertebral osteophyte			
subjects affected / exposed	0 / 191 (0.00%)	1 / 186 (0.54%)	0 / 185 (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
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 186 (0.54%)	0 / 185 (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
Pneumonia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Sepsis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 186 (0.00%)	0 / 185 (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

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	NLX 48 Safety	NLX 24 Safety	Placebo Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 191 (51.31%)	107 / 186 (57.53%)	95 / 185 (51.35%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 191 (2.62%)	10 / 186 (5.38%)	4 / 185 (2.16%)
occurrences (all)	5	10	6
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	8 / 191 (4.19%)	9 / 186 (4.84%)	3 / 185 (1.62%)
occurrences (all)	8	9	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 191 (6.28%)	11 / 186 (5.91%)	6 / 185 (3.24%)
occurrences (all)	14	12	7
Abdominal pain			
subjects affected / exposed	6 / 191 (3.14%)	6 / 186 (3.23%)	5 / 185 (2.70%)
occurrences (all)	7	6	5
Nausea			
subjects affected / exposed	9 / 191 (4.71%)	5 / 186 (2.69%)	3 / 185 (1.62%)
occurrences (all)	10	5	3
Constipation			
subjects affected / exposed	8 / 191 (4.19%)	3 / 186 (1.61%)	3 / 185 (1.62%)
occurrences (all)	10	3	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 191 (3.66%)	9 / 186 (4.84%)	9 / 185 (4.86%)
occurrences (all)	8	9	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

NA

Notes: