



## Clinical trial results:

### Open-label, uncontrolled trial to evaluate pharmacokinetics of naloxone in children from 4 to less than 18 years of age with opioid-induced constipation

#### Summary

EudraCT number	2015-002310-72
Trial protocol	DE HU CZ
Global end of trial date	27 December 2019

#### Results information

Result version number	v1 (current)
This version publication date	19 September 2020
First version publication date	19 September 2020

#### Trial information

##### Trial identification

Sponsor protocol code	0201/DEV
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##### 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. 12D, Pratteln, Switzerland, 4133
Public contact	Sponsor Clinical Team, Develco Pharma Schweiz AG, +41 614255020, info@develco.ch
Scientific contact	Clinical Development, Develco Pharma Schweiz AG, +41 614255020, clinicaldevelopment@develco.ch

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001567-PIP01-13
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	27 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 December 2019
Global end of trial reached?	Yes
Global end of trial date	27 December 2019
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To characterise the pharmacokinetics (PK) of naloxone-3-glucuronide (NLX-3-G), in children (4 to less than 18 years) with opioid-induced constipation (OIC) after single oral dose of one naloxone (NLX) HCI prolonged release (PR) tablet.

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:

The individual opioid therapy, i.e. any opioid (WHO step II and III) including low level opioids, except any combination formulations (including morphine and naloxone) for the treatment of pain.

Evidence for comparator: -

Actual start date of recruitment	12 October 2016
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: 1
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 1
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	3
Adolescents (12-17 years)	5

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects between 4 to less than 18 years of age with pain due to underlying malignant or non malignant disease, requiring or about to require opioid treatment and diagnosed with OIC or expected to develop constipation after initiation of opioid treatment were included in this trial.

### Period 1

Period 1 title	PK Day
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Group A

Arm description:

NLX HCl PR, 6 mg tablets

At Visit 2 the subjects were centrally distributed to achieve a 1:1 ratio for evaluation of PK data

After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (6 mg twice daily [TDD 12 mg])

Arm type	Experimental
Investigational medicinal product name	Naloxone HCl 6 mg PR tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects took one single oral dose of NLX HCl PR tablets at their assigned tablet strength on Day 1.

<b>Arm title</b>	Group B
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Arm description:

NLX HCl PR, 12 mg tablets

At Visit 2 the subjects were centrally distributed to achieve a 1:1 ratio for evaluation of PK data

After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (12 mg twice daily [TDD 24 mg]).

Arm type	Experimental
Investigational medicinal product name	Naloxone HCl 12 mg PR tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects took one single oral dose of NLX HCl PR tablets at their assigned tablet strength on Day 1.

Number of subjects in period 1 <sup>[1]</sup>	Group A	Group B
Started	3	3
Completed	3	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 8 subjects were enrolled in the study (signed ICF, Enrolled Set). Out of these, 2 subjects were screening failures.

## Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Group A

Arm description:

NLX HCl PR, 6 mg tablets

At Visit 2 the subjects were centrally distributed to achieve a 1:1 ratio for evaluation of PK data  
After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (6 mg twice daily [TDD 12 mg])

Arm type	Experimental
Investigational medicinal product name	Naloxone HCl 6 mg PR tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects took one single oral dose of NLX HCl PR tablets at their assigned tablet strength on Day 1.  
After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (Group A: 6 mg twice daily [TDD 12 mg]).

<b>Arm title</b>	Group B
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Arm description:

NLX HCl PR, 12 mg tablets

At Visit 2 the subjects were centrally distributed to achieve a 1:1 ratio for evaluation of PK data  
After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (12 mg twice daily [TDD 24 mg]).

Arm type	Experimental
Investigational medicinal product name	Naloxone HCl 12 mg PR tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects took one single oral dose of NLX HCl PR tablets at their assigned tablet strength on Day 1.  
After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (Group B: 12 mg twice daily [TDD 24 mg]).

Number of subjects in period 2 <sup>[2]</sup>	Group A	Group B
Started	1	2
Completed	1	2

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Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Extension period was optional. Out of 6 subjects that completed the PK day, 3 subjects entered and completed the extension period as intended (i.e. as long as individual opioid treatment was ongoing).

## Baseline characteristics

### Reporting groups

Reporting group title	PK Day
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Reporting group description: -

Reporting group values	PK Day	Total	
Number of subjects	6	6	
Age categorical			
Units: Subjects			
Children (2-11 years)	1	1	
Adolescents (12-17 years)	5	5	
Age continuous			
Units: years			
arithmetic mean	13.3		
standard deviation	± 3.93	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	3	3	

### Subject analysis sets

Subject analysis set title	PK Set
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Subject analysis set type	Per protocol
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Subject analysis set description:

The pharmacokinetics set is defined as all safety set subjects for whom at least one evaluable PK parameter is available.

Subject analysis set title	Safety Set
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety set is defined as all subjects who received at least one dose of IMP.

Reporting group values	PK Set	Safety Set	
Number of subjects	6	6	
Age categorical			
Units: Subjects			
Children (2-11 years)	1	1	
Adolescents (12-17 years)	5	5	
Age continuous			
Units: years			
arithmetic mean	13.3	13.3	
standard deviation	± 3.93	± 3.93	
Gender categorical			
Units: Subjects			
Female			
Male			

## End points

### End points reporting groups

Reporting group title	Group A
Reporting group description: NLX HCl PR, 6 mg tablets At Visit 2 the subjects were centrally distributed to achieve a 1:1 ratio for evaluation of PK data After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (6 mg twice daily [TDD 12 mg])	
Reporting group title	Group B
Reporting group description: NLX HCl PR, 12 mg tablets At Visit 2 the subjects were centrally distributed to achieve a 1:1 ratio for evaluation of PK data After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (12 mg twice daily [TDD 24 mg]).	
Reporting group title	Group A
Reporting group description: NLX HCl PR, 6 mg tablets At Visit 2 the subjects were centrally distributed to achieve a 1:1 ratio for evaluation of PK data After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (6 mg twice daily [TDD 12 mg])	
Reporting group title	Group B
Reporting group description: NLX HCl PR, 12 mg tablets At Visit 2 the subjects were centrally distributed to achieve a 1:1 ratio for evaluation of PK data After completion of PK blood sampling, the subjects entering the extension period started with IMP intake twice daily on Day 2 (12 mg twice daily [TDD 24 mg]).	
Subject analysis set title	PK Set
Subject analysis set type	Per protocol
Subject analysis set description: The pharmacokinetics set is defined as all safety set subjects for whom at least one evaluable PK parameter is available.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety set is defined as all subjects who received at least one dose of IMP.	

### Primary: AUC(0-t ) of naloxone

End point title	AUC(0-t ) of naloxone <sup>[1]</sup>
End point description: Area under the plasma concentration time curve from the first time point [t=0] until last measured time point [t(last)] (AUC(0-t )), measured in ng/ml h Adjusted to 6 mg dose and 50 kg weight	
End point type	Primary
End point timeframe: Single dose PK (starting on Day 1/Visit 2) during 24 hours (at pre-dose and 30 min, 60 min, 90 min, 2 h, 9 h and 24 h, after intake of NLX HCl PR tablets	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive statistic was foreseen.	



End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: ng/ml h				
arithmetic mean (standard deviation)	0.363 (± 0.4249)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of naloxone

End point title	Cmax of naloxone <sup>[2]</sup>
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End point description:

Maximum plasma concentration after first dose (Cmax)  
adjusted to 6mg dose and 50 kg weight

End point type	Primary
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End point timeframe:

Single dose PK (starting on Day 1/Visit 2) during 24 hours (at pre-dose and 30 min, 60 min, 90 min, 2 h, 9 h and 24 h, after intake of NLX HCl PR tablets

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistic was foreseen.

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: unit(s)				
arithmetic mean (standard deviation)	0.05897 (± 0.082722)			

## Statistical analyses

No statistical analyses for this end point

### Primary: tmax of naloxone

End point title	tmax of naloxone <sup>[3]</sup>
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End point description:

Time until Cmax (tmax)  
adjusted to 6 mg dose and 50 kg weight

End point type	Primary
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End point timeframe:

Single dose PK (starting on Day 1/Visit 2) during 24 hours (at pre-dose and 30 min, 60 min, 90 min, 2 h, 9 h and 24 h, after intake of NLX HCl PR tablets

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistic was foreseen.

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: unit(s)				
arithmetic mean (standard deviation)	7.66 (± 8.960)			

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC(0-t ) of naloxone-3-glucuronide

End point title	AUC(0-t ) of naloxone-3-glucuronide <sup>[4]</sup>
End point description:	
Adjusted to 6 mg dose and 50 kg weight	
End point type	Primary
End point timeframe:	
Single dose PK (starting on Day 1/Visit 2) during 24 hours (at pre-dose and 30 min, 60 min, 90 min, 2 h, 9 h and 24 h, after intake of NLX HCl PR tablets	

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistic was foreseen.

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: ng/ml h				
arithmetic mean (standard deviation)	140.553 (± 77.3845)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of naloxone-3-glucuronide

End point title	Cmax of naloxone-3-glucuronide <sup>[5]</sup>
End point description:	
Adjusted to 6 mg dose and 50 kg weight	
End point type	Primary
End point timeframe:	
Single dose PK (starting on Day 1/Visit 2) during 24 hours (at pre-dose and 30 min, 60 min, 90 min, 2 h, 9 h and 24 h, after intake of NLX HCl PR tablets	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistic was foreseen.

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: ng/ml h				
arithmetic mean (standard deviation)	16.400 ( $\pm$ 13.2200)			

## Statistical analyses

No statistical analyses for this end point

## Primary: tmax of naloxone-3-glucuronide

End point title	tmax of naloxone-3-glucuronide <sup>[6]</sup>
End point description:	
Adjusted to 6 mg dose and 50 kg weight	
End point type	Primary
End point timeframe:	
Single dose PK (starting on Day 1/Visit 2) during 24 hours (at pre-dose and 30 min, 60 min, 90 min, 2 h, 9 h and 24 h, after intake of NLX HCl PR tablets	

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistic was foreseen.

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: ng/ml h				
arithmetic mean (standard deviation)	4.09 ( $\pm$ 3.970)			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs with onset or worsening after first intake of IMP until 14 days after last intake of IMP

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Safety Set
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Reporting group description: -

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Musculoskeletal and connective tissue disorders Osteonecrosis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2018	The main changes of the Clinical Trial Protocol (CTP), Final Version 2.0, 12-JUL-2018 were: the subjects' age range broadened to range from 4 to less than 18 years, the primary objective was changed from steady state PK to PK of naloxone-3-glucuronide after single dose, as a result the treatment period was reduced to one PK day. Standardised laxative rescue medication was removed, instead subjects were allowed to take concomitant laxatives according to their individual standard of care. Study endpoints and objectives as well as statistical methods were adapted accordingly.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 April 2018	Due to notable modifications of the primary objective, the trial was temporarily set on hold on 17-APR-2018, during PIP and protocol modification. The trial was re-started after receipt of approvals for the CTP Final Version 2.0, dated 12-JUL-2018 by the responsible independent ethics committees (IECs) and competent authorities (CAs).	12 July 2018

Notes:

### Limitations and caveats

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

As a matter of the challenging and unsuccessful recruitment on CTP Final Version 1.0, 11-NOV-2015, a RfM was submitted to the EMA (PDCO) to agree on potential changes of the CTP, to improve recruitment and facilitate the conduct of the clinical trial

Notes: