Clinical trial results:
Prospective, single-blind, placebo-controlled, three-treatment, three-period, adaptive multi-centre Phase IIa (proof-of-concept) trial to investigate the efficacy, safety, and tolerability of Ketamine HCl PR tablets in patients with chronic non-malignant neuropathic pain

Summary

EudraCT number	2014-004535-40
Trial protocol	HU DE
Global end of trial date	31 January 2017

Results information

Result version number	v1 (current)
This version publication date	10 April 2020
First version publication date	10 April 2020

Trial information

Trial identification

Sponsor protocol code	0189/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	Clinical Trial Manager, Develco Pharma Schweiz AG, 0041 614255020, k.schmid@develco.ch
Scientific contact	Clinical Trial Manager, Develco Pharma Schweiz AG, 0041 614255020, k.schmid@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	23 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2016
Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of Ketamine HCl PR tablets administered twice daily as add-on therapy to the individual standard treatment regimen of each patient in comparison to placebo in the relief of chronic non-malignant neuropathic pain as determined by absolute changes in the "current" pain intensity (PI) score on the visual analogue scale (VAS)

Protection of trial subjects:

Due to the prolonged release formulation used in this study the risks and frequencies of adverse reactionswere extected to be remarkably lower and with milder severities as compared to formulations for injection. These risks were further minimised by regular contact between the patient and investigator and by close safety monitoring.

Background therapy:

The patients continued their previous individual standard medication and regimen for the treatment of pain.

Evidence for comparator: -

Actual start date of recruitment	08 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	43

From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients ≥18 years of age with a documented history of chronic non-malignant neuropathic pain and with inadequate pain control

Pre-assignment

Screening details:

A total of 70 subjects were screened. 16 subjects were screening failures.

Pre-assignment period milestones

Number of subjects started	70[1]
Number of subjects completed	54

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Other: 15

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 in the trial is the number of subjects assigned to treatment.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Overall - Low

Arm description:

Individual standard treatment of pain plus Ketamine HCl PR twice daily

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

Dosage and administration details:

Period 1: Ketamine HCl PR Placebo tablets, one tablet twice daily
Period 2 : Ketamine HCl 40 mg PR tablets, one tablet twice daily (TDD: 80 mg)
Period 3: Ketamine HCl 80 mg PR tablets, one tablet twice daily (TDD: 160 mg)

Arm title	Overall - High

Arm description:

Individual standard treatment of pain plus Ketamine HCl PR twice daily

Arm type	Experimental

Investigational medicinal product name	Ketamine HCl PR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Period 1: Ketamine HCl PR Placebo tablets, one tablet twice daily
Period 2 : Ketamine HCl 40+60 mg PR tablets, two tablets twice daily (TDD: 240 mg)
Period 3: Ketamine HCl 80 mg PR tablets, two tablets twice daily (TDD: 320 mg)

Number of subjects in period 1	Overall - Low	Overall - High
Started	25	29
Completed	23	25
Not completed	2	4
Adverse event, non-fatal	-	2
Other	2	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall - Low
Reporting group description:	
Individual standard treatment of pain plus Ketamine HCl PR twice daily	
Reporting group title	Overall - High
Reporting group description:	
Individual standard treatment of pain plus Ketamine HCl PR twice daily	

Reporting group values	Overall - Low	Overall - High	Total
Number of subjects	25	29	54
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	18	25	43
From 65 – 84 years	7	4	11
Over 85 years	0	0	0
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	52.8	52.9	
standard deviation	± 15.46	± 12.51	-
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	15	17	32
Male	10	12	22

End points

End points reporting groups

Reporting group title	Overall - Low
Reporting group description:	
Individual standard treatment of pain plus Ketamine HCl PR twice daily	
Reporting group title	Overall - High
Reporting group description:	
Individual standard treatment of pain plus Ketamine HCl PR twice daily	
Subject analysis set title	Overall - Low x Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of IMP.	
Subject analysis set title	Overall - High x Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of IMP.	
Subject analysis set title	Overall - Low x FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who received at least one dose of Ketamine HCl PR tablets and with at least one current pain intensity assessment during Period 2 of the single-blind treatment phase.	
Subject analysis set title	Overall - High x FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who received at least one dose of Ketamine HCl PR tablets and with at least one current pain intensity assessment during Period 2 of the single-blind treatment phase.	

Primary: Mean current PI change

End point title	Mean current PI change
End point description:	
Absolute change from baseline in current PI on 0 - 100 mm VAS (mean of all current PIs of the last four days of each treatment period) after Ketamine HCl PR Placebo tablets versus Ketamine HCl PR tablets.	
End point type	Primary
End point timeframe:	
Baseline up to three weeks in single-blind treatment phase	

End point values	Overall - Low x FAS	Overall - High x FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	27		
Units: mm				
number (standard deviation)				
mm	23	26		

Statistical analyses

Statistical analysis title	Statistical Analysis of mean current PI change

Statistical analysis description:

Absolute changes in mean current PI scores are analysed via a mixed model for repeated measures (MMRM) with baseline mean current PI as a covariate, period and stage as a fixed factors and stage-by-period interaction

Comparison groups	Overall - Low x FAS v Overall - High x FAS
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1547 [1]
Method	Mixed models analysis
Parameter estimate	LS Means Difference
Point estimate	-4.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	1.7

Notes:

[1] - Overall - High x FAS Period 3 - Period 1

Statistical analysis title	Statistical Analysis of mean current PI change

Statistical analysis description:

Absolute changes in mean current PI scores are analysed via a mixed model for repeated measures (MMRM) with baseline mean current PI as a covariate, period and stage as a fixed factors and stage-by-period interaction

Comparison groups	Overall - Low x FAS v Overall - High x FAS
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0034 [2]
Method	Mixed models analysis
Parameter estimate	LS Means Difference
Point estimate	-9.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.41
upper limit	-3.45

Notes:

[2] - Overall - Low x FAS Period 3 - Period 1

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	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

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

Serious adverse events	Overall - High x Safety	Overall - Low x Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Overall - High x Safety	Overall - Low x Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 29 (51.72%)	12 / 25 (48.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 29 (3.45%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 29 (3.45%)	3 / 25 (12.00%)	
occurrences (all)	1	4	
Pain			

subjects affected / exposed	0 / 29 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Sleep Disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	4 / 29 (13.79%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	2 / 29 (6.90%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Biopsy Peripheral Nerve			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Blood Pressure Increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Heart Rate Increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Transaminases Increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	

Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 29 (20.69%)	1 / 25 (4.00%)	
occurrences (all)	7	1	
Headache			
subjects affected / exposed	4 / 29 (13.79%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Tension Headache			
subjects affected / exposed	0 / 29 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 29 (10.34%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Constipation			

subjects affected / exposed	1 / 29 (3.45%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Abdominal Pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Abdominal Pain Upper			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Dry Mouth			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Rash Pruritic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 29 (6.90%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Limb Discomfort			

subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Bronchitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2015	Global Protocol Amendment No. 1 This protocol amendment provides the IMP dose specification for Stage 2 of the 0189/DEV trial outlined in Protocol Final Version 1.0 (21-JAN-2015)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported