



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 reactions were expected 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 occurrences (all) | 0 / 29 (0.00%) 0 | 3 / 25 (12.00%) 3 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 25 (0.00%) 0 | |
| Psychiatric disorders Sleep Disorder subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 25 (0.00%) 0 | |
| Investigations Hepatic Enzyme Increased subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 4 | 1 / 25 (4.00%) 1 | |
| Gamma-Glutamyltransferase Increased subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 25 (0.00%) 0 | |
| Alanine Aminotransferase Increased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 25 (0.00%) 0 | |
| Biopsy Peripheral Nerve subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 25 (0.00%) 0 | |
| Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 25 (0.00%) 0 | |
| Blood Pressure Increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 25 (4.00%) 1 | |
| Heart Rate Increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 25 (4.00%) 1 | |
| Transaminases Increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 25 (4.00%) 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 | |
| Gastroesophageal 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 occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 25 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 0 / 29 (0.00%) 0 1 / 29 (3.45%) 1 | 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1 0 / 25 (0.00%) 0 | |
| Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 25 (4.00%) 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