# Clinical trial results:
# Spinal anaesthesia with Chloroprocaine HCl 1% for elective lower limb procedures of short duration: a prospective, randomised, observer-blind study in adult patients

## Summary

| | |
|---|---|
| EudraCT number | 2014-003778-17 |
| Trial protocol | IT |
| Global end of trial date | 02 December 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 August 2021 |
| First version publication date | 21 August 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CHL.1/02-2014 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02481505 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Study: CRO-14-122 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Sintetica SA |
| Sponsor organisation address | Via Penate 5, Mendrisio, Switzerland, 6850 |
| Public contact | Study Management, CROSS S.A., 0041 916300510, corporate@croalliance.com |
| Scientific contact | Study Management, CROSS S.A., 0041 916300510, corporate@croalliance.com |

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 | 02 December 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 02 December 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the effect of 3 doses of Chloroprocaine HCl 1% (30, 40 and 50 mg) for spinal anaesthesia in adult patients undergoing short duration elective surgery of the lower limb, in terms of time to complete regression of spinal block

Protection of trial subjects:

According to exclusion criterion nr 10:  Chronic pain syndromes: patients with chronic pain syndromes (taking opioids, antidepressants, anticonvulsant agents or chronic analgesic therapy).
After the lumbar puncture and after verifying the spontaneous flow of liquor at the beginning and at the end of the procedure, two short aspirations will be done to verify the proper positioning of the needle. Barbotage must be avoided. In case of incomplete anaesthesia, sedative, analgesics or anaesthetics should be administered.
Post-operative analgesia will be given to all patients, if necessary, according to the hospital standard procedures.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 July 2015 |
| 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 | Italy: 46 |
| Worldwide total number of subjects | 46 |
| EEA total number of subjects | 46 |

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) | 46 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The enrollment period was around 5 months.
Inclusion criteria:
1.male/female patients, 18-65 year old, scheduled for short duration (< 40 min) lower limb surgery requiring ≥ T12 metameric level of sensory block
2.BMI: 18-32 kg/m2 inclusive
3.(ASA) physical status I/II
4.written ICF before any study procedures
5.full procedure comprehension

### Pre-assignment

Screening details:

There were no screening requirement other that the inclision/exclusion criteria.
46 patients were included in the study and randomized. 45 patients were treated and completed the study. All of them were considered in the full analysis. 1 patient was randomized but not treated due to lack of compliance, not included in the analysis.

### Period 1

| | |
|---|---|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Investigator[1] |

Blinding implementation details:

For completeness, the study was observer blind, so the physician placing the spinal block will not be further involved in patient's care and data recording. The assessment on patients was done by blinded Investigator

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Dose 1 |

Arm description:

patients receiving 30 mg of Chloroprocaine HCl 1% solution for injection

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Chloroprocaine HCl 1% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intrathecal use |

Dosage and administration details:

30 mg of Chloroprocaine HCl 1% for spinal anaesthesia

| | |
|---|---|
| **Arm title** | Dose 2 |

Arm description:

Patients receiving 40 mg of Chloroprocaine HCl 1% solution for injection

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Chloroprocaine HCl 1% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intrathecal use |

Dosage and administration details:

40 mg of Chloroprocaine HCl 1% for spinal anaesthesia

| **Arm title** | Dose 3 |
|---|---|

Arm description:

Patients receiving 50 mg of Chloroprocaine HCl 1% solution for injection

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Chloroprocaine HCl 1% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intrathecal use |

Dosage and administration details:

50 mg of Chloroprocaine HCl 1% for spinal anaesthesia

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: For completeness, the study was observer blind, so the physician placing the spinal block will not be further involved in patient's care and data recording. The assessment on patients was done by blinded Investigator

| **Number of subjects in period 1[2]** | Dose 1 | Dose 2 | Dose 3 |
|---|---|---|---|
| Started | 15 | 15 | 15 |
| Completed | 15 | 15 | 15 |

Notes:

[2] - 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: 46 patients were included in the study and randomized. 45 patients were treated and completed the study. All of them were considered in the full analysis. 1 patient was randomized but not treated due to lack of compliance, not included in the analysis.

Not able to properly amend this section

## Baseline characteristics

### Reporting groups

| Reporting group title | overall trial |
|---|---|

Reporting group description: -

| Reporting group values | overall trial | Total | |
|---|---|---|---|
| Number of subjects | 45 | 45 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 45 | 45 | |
| From 65-84 years | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 40.6 | | |
| standard deviation | ± 12.5 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 18 | 18 | |
| Male | 27 | 27 | |

### Subject analysis sets

| Subject analysis set title | Full Analysis Set (FAS) |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

all randomised patients who fulfil the study protocol requirements in terms of study anaesthetic administration. Missing values of time to complete spinal block regression (Tea) will be replaced with the highest Tea detected in the corresponding treatment group. This analysis set will be used for sensitivity analysis.

| Subject analysis set title | Per Protocol set (PP) |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

all randomised patients who fulfil the study protocol requirements in terms of anaesthetic administration and primary efficacy evaluation, with no major deviations that could affect the primary efficacy results. This analysis set will be used for the primary efficacy analysis.

| Subject analysis set title | PK Set 1 (PK 1) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

the PK set 1 will include all randomised patients who fulfil the study protocol requirements in terms of anaesthetic administration and have at least one post-dose blood PK sample collected.

| Subject analysis set title | PK Set 2 (PK 2) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

the PK set 2 will include all randomised patients who fulfil the study protocol requirements in terms of anaesthetic administration and have the urine for PK analysis collected.

| Subject analysis set title | Safety set |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

all patients who receive at least one dose of the investigational medicinal product. This analysis set will be used for the safety analyses.

| | |
|---|---|
| Subject analysis set title | Enrolled set |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All enrolled subjects. This analysis set was used for demographic, baseline and background characteristics.

| **Reporting group values** | Full Analysis Set (FAS) | Per Protocol set (PP) | PK Set 1 (PK 1) |
|---|---|---|---|
| Number of subjects | 45 | 39 | 45 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 45 | 39 | 45 |
| From 65-84 years | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 40.6 | 41.3 | 40.6 |
| standard deviation | ± 12.6 | ± 12.5 | ± 12.6 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 18 | 17 | 18 |
| Male | 27 | 22 | 27 |

| **Reporting group values** | PK Set 2 (PK 2) | Safety set | Enrolled set |
|---|---|---|---|
| Number of subjects | 43 | 45 | 46 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 43 | 45 | 46 |
| From 65-84 years | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 40.7 | 40.6 | 40.6 |
| standard deviation | ± 12.9 | ± 12.6 | ± 12.5 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 17 | 18 | 19 |
| Male | 26 | 27 | 27 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Dose 1 |
| Reporting group description: | |
| patients receiving 30 mg of Chloroprocaine HCl 1% solution for injection | |
| Reporting group title | Dose 2 |
| Reporting group description: | |
| Patients receiving 40 mg of Chloroprocaine HCl 1% solution for injection | |
| Reporting group title | Dose 3 |
| Reporting group description: | |
| Patients receiving 50 mg of Chloroprocaine HCl 1% solution for injection | |
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| all randomised patients who fulfil the study protocol requirements in terms of study anaesthetic administration. Missing values of time to complete spinal block regression (Tea) will be replaced with the highest Tea detected in the corresponding treatment group. This analysis set will be used for sensitivity analysis. | |
| Subject analysis set title | Per Protocol set (PP) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| all randomised patients who fulfil the study protocol requirements in terms of anaesthetic administration and primary efficacy evaluation, with no major deviations that could affect the primary efficacy results. This analysis set will be used for the primary efficacy analysis. | |
| Subject analysis set title | PK Set 1 (PK 1) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| the PK set 1 will include all randomised patients who fulfil the study protocol requirements in terms of anaesthetic administration and have at least one post-dose blood PK sample collected. | |
| Subject analysis set title | PK Set 2 (PK 2) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| the PK set 2 will include all randomised patients who fulfil the study protocol requirements in terms of anaesthetic administration and have the urine for PK analysis collected. | |
| Subject analysis set title | Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| all patients who receive at least one dose of the investigational medicinal product. This analysis set will be used for the safety analyses. | |
| Subject analysis set title | Enrolled set |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All enrolled subjects. This analysis set was used for demographic, baseline and background characteristics. | |

### Primary: to evaluate the efficacy of the 3 Chloroprocaine HCl 1% doses D1, D2 and D3 in terms of time to complete regression of spinal block (Tea) (i.e. end of anaesthesia)_FAS

| | |
|---|---|
| End point title | to evaluate the efficacy of the 3 Chloroprocaine HCl 1% doses D1, D2 and D3 in terms of time to complete regression of spinal block (Tea) (i.e. end of anaesthesia)_FAS |

End point description:

Time to regression of spinal block (Tea), defined as the time when Bromage score returns to 0 and

sensitive perception returns to S1.

| End point type | Primary |
|---|---|

End point timeframe:

at visit 2/day 1

| **End point values** | Dose 1 | Dose 2 | Dose 3 | Full Analysis Set (FAS) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: time (hh:mm) | | | | |
| arithmetic mean (standard deviation) | 1.761 (± 0.348) | 2.127 (± 0.457) | 2.229 (± 0.379) | 2.039 (± 0.438) |

| **Attachments (see zip file)** | primary and secondary efficacy variables/primary and |
|---|---|

## Statistical analyses

| **Statistical analysis title** | comparison of time to events_overall comparison |
|---|---|

Statistical analysis description:

Tea, Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| Comparison groups | Dose 3 v Dose 2 v Dose 1 |
|---|---|
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | = 0.0092 [2] |
| Method | Kruskal-wallis |

Notes:

[1] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[2] - statistically significant

| **Statistical analysis title** | comparison of time to events_D1 vs D3 |
|---|---|

Statistical analysis description:

Tea, Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| Comparison groups | Dose 1 v Dose 3 |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[3] |
| P-value | = 0.0063 [4] |
| Method | Wilcoxon rank-sum test |

Notes:

[3] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[4] - statistically significant

| **Statistical analysis title** | comparison of time to events_D2 vs D3 |
|---|---|

Statistical analysis description:

Tea, Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 3 v Dose 2 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[5] |
| P-value | = 0.7423 [6] |
| Method | Wilcoxon rank-sum test |

Notes:

[5] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[6] - not statistically significant

| **Statistical analysis title** | comparison of time to events_D1 vs D2 |
|---|---|

Statistical analysis description:

Tea, Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 2 v Dose 1 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| P-value | = 0.0344 [8] |
| Method | Wilcoxon rank-sum test |

Notes:

[7] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison

4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[8] - statistically significant

## Primary: to evaluate the efficacy of the 3 Chloroprocaine HCl 1% doses D1, D2 and D3 in terms of time to complete regression of spinal block (Tea) (i.e. end of anaesthesia)_PP

| | |
|---|---|
| End point title | to evaluate the efficacy of the 3 Chloroprocaine HCl 1% doses D1, D2 and D3 in terms of time to complete regression of spinal block (Tea) (i.e. end of anaesthesia)_PP |

End point description:

Time to regression of spinal block (Tea), defined as the time when Bromage score returns to 0 and sensitive perception returns to S1.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

at visit 2 / day 1

| End point values | Dose 1 | Dose 2 | Dose 3 | Per Protocol set (PP) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 12 | 13 | 14 | 39 |
| Units: time (hh:mm) | | | | |
| arithmetic mean (standard deviation) | 1.813 (± 0.333) | 2.119 (± 0.394) | 2.218 (± 0.391) | 2.061 (± 0.404) |

| | |
|---|---|
| **Attachments (see zip file)** | primary and secondary efficacy variables.PNG |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | comparison of time to events_overall comparison |

Statistical analysis description:

Tea, Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 3 v Dose 2 v Dose 1 |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | other[9] |
| P-value | = 0.0368 [10] |
| Method | Kruskal-wallis |

Notes:

[9] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison

Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[10] - statistically significant

| **Statistical analysis title** | comparison of time to events_D1 vs D3 |
|---|---|

Statistical analysis description:

Tea, Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| Comparison groups | Dose 1 v Dose 3 |
|---|---|
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other[11] |
| P-value | = 0.0259 [12] |
| Method | Wilcoxon rank-sum test |

Notes:

[11] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[12] - statistically significant

| **Statistical analysis title** | comparison of time to events_D2 vs D3 |
|---|---|

Statistical analysis description:

Tea, Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| Comparison groups | Dose 3 v Dose 2 |
|---|---|
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other[13] |
| P-value | = 0.8475 [14] |
| Method | Wilcoxon rank-sum test |

Notes:

[13] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[14] - not statistically significant

| **Statistical analysis title** | comparison of time to events_D1 vs D2 |
|---|---|

Statistical analysis description:

Tea, Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| Comparison groups | Dose 2 v Dose 1 |
|---|---|
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | other[15] |
| P-value | = 0.0553 [16] |
| Method | Wilcoxon rank-sum test |

Notes:

[15] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[16] - not statistically significant

## Secondary: To evaluate the efficacy of three Chloroprocaine HCl 1% doses at several timepoints_FAS

| End point title | To evaluate the efficacy of three Chloroprocaine HCl 1% doses at several timepoints_FAS |
|---|---|

End point description:

Tsb: Time to onset of sensory block (min)
Tmb: Time to onset of motor block (min)
Trs: Time to readiness for surgery (min)
Trmb: Time to resolution of motor block (h)
Tua: Time to unassisted ambulation (h)
TS1: Time to resolution of sensory block to S1 (h) (where S1 is the 1st sacral dermatomal level)
TSBmax: Time to maximum level of sensory block (min)
Trd: Time to regression of two dermatomers with respect to the maximum level of sensory block (h)
Tuv: Time to first spontaneous urine voiding (h)
Tra: Time to administration of rescue anaesthesia or rescue analgesia (h)
Tpa: Time to first post-operative analgesia (h)
Thd: Time to eligibility for home discharge (h)

| End point type | Secondary |
|---|---|

End point timeframe:

At visit 2/day 1, timepoints described in the description since no enough space is foreseen here

| **End point values** | Dose 1 | Dose 2 | Dose 3 | Full Analysis Set (FAS) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: time (h or m) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Tsb: Time to onset of sensory block (min) | 5.4 (± 3.0) | 6.6 (± 3.4) | 4.8 (± 2.0) | 5.6 (± 2.8) |
| Tmb: Time to onset of motor block (min) | 6.3 (± 3.2) | 6.0 (± 3.3) | 4.4 (± 2.3) | 5.6 (± 3.0) |

| | | | | |
|---|---|---|---|---|
| Trs: Time to readiness for surgery (min) | 8.0 (± 4.1) | 7.9 (± 4.7) | 5.3 (± 2.0) | 7.1 (± 3.9) |
| Trmb: Time to resolution of motor block (h) | 1.438 (± 0.409) | 1.480 (± 0.400) | 1.661 (± 0.459) | 1.526 (± 0.425) |
| Tua: Time to unassisted ambulation (h) | 2.662 (± 0.789) | 3.361 (± 1.120) | 3.213 (± 0.856) | 3.079 (± 0.960) |
| TS1: Time to resolution of sensory block to S1 (h) | 1.761 (± 0.348) | 2.127 (± 0.457) | 2.195 (± 0.386) | 2.028 (± 0.435) |
| TSBmax: Time to maximum level of sensory block (mi | 0.224 (± 0.140) | 0.235 (± 0.077) | 0.234 (± 0.098) | 0.231 (± 0.106) |
| Trd: Time to regression of two dermatomers with re | 0.687 (± 0.361) | 0.851 (± 0.468) | 0.695 (± 0.290) | 0.744 (± 0.379) |
| Tuv: Time to first spontaneous urine voiding (h) | 2.530 (± 0.761) | 3.361 (± 1.120) | 3.067 (± 0.755) | 2.986 (± 0.941) |
| Tra: Time to administration of rescue anaesthesia | 0.717 (± 0.397) | 0.315 (± 0.049) | 0 (± 0) | 0.556 (± 0.358) |
| Tpa: Time to first post-operative analgesia (h) | 8.186 (± 10.815) | 2.928 (± 1.228) | 2.988 (± 1.167) | 4.918 (± 6.996) |
| Thd: Time to eligibility for home discharge (h) | 3.021 (± 1.012) | 3.545 (± 1.281) | 3.530 (± 0.887) | 3.366 (± 1.076) |

| | |
|---|---|
| **Attachments (see zip file)** | p-values efficacy variables.PNG |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | comparison of time to events_overall comparison |

Statistical analysis description:

Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 3 v Dose 2 v Dose 1 |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | other[17] |
| P-value | = 0.3732 [18] |
| Method | Kruskal-wallis |

Notes:

[17] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[18] - p-value for Tsb
not statistically significant.
The p-values for the other parameters are listed in the picture attached in the previous page

| | |
|---|---|
| **Statistical analysis title** | comparison of time to events_D1 vs D3 |

Statistical analysis description:

Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.

Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 1 v Dose 3 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[19] |
| P-value | = 0.6862 [20] |
| Method | Wilcoxon rank-sum test |

Notes:

[19] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[20] - p-value for Tsb
not statistically significant.
The p-values for the other parameters are listed in the picture attached in the previous page

| **Statistical analysis title** | comparison of time to events_D2 vs D3 |
|---|---|

Statistical analysis description:

Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 2 v Dose 3 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[21] |
| P-value | = 0.1712 [22] |
| Method | Wilcoxon rank-sum test |

Notes:

[21] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[22] - p-value for Tsb
not statistically significant.
The p-values for the other parameters are listed in the picture attached in the previous page

| **Statistical analysis title** | comparison of time to events_D1 vs D2 |
|---|---|

Statistical analysis description:

Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 2 v Dose 1 |

| | |
|---|---|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[23] |
| P-value | = 0.4058 [24] |
| Method | Wilcoxon rank-sum test |

Notes:

[23] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[24] - p-value for Tsb
not statistically significant.
The p-values for the other parameters are listed in the picture attached in the previous page

## Secondary: To evaluate the efficacy of three Chloroprocaine HCl 1% doses at several timepoints_PP

| | |
|---|---|
| End point title | To evaluate the efficacy of three Chloroprocaine HCl 1% doses at several timepoints_PP |

End point description:

Tsb: Time to onset of sensory block (min)
Tmb: Time to onset of motor block (min)
Trs: Time to readiness for surgery (min)
Trmb: Time to resolution of motor block (h)
Tua: Time to unassisted ambulation (h)
TS1: Time to resolution of sensory block to S1 (h) (where S1 is the 1st sacral dermatomal level)
TSBmax: Time to maximum level of sensory block (min)
Trd: Time to regression of two dermatomers with respect to the maximum level of sensory block (h)
Tuv: Time to first spontaneous urine voiding (h)
Tra: Time to administration of rescue anaesthesia or rescue analgesia (h)
Tpa: Time to first post-operative analgesia (h)
Thd: Time to eligibility for home discharge (h)

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

At visit 2/day 1, timepoints described in the description since no enough space is foreseen here

| End point values | Dose 1 | Dose 2 | Dose 3 | Per Protocol set (PP) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 12 | 13 | 14 | 39 |
| Units: time (h or m) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Tsb: Time to onset of sensory block (min) | 5.3 (± 3.1) | 6.9 (± 3.2) | 4.6 (± 1.8) | 5.6 (± 2.9) |
| Tmb: Time to onset of motor block (min) | 6.0 (± 3.1) | 6.2 (± 3.3) | 4.4 (± 2.4) | 5.5 (± 3.0) |
| Trs: Time to readiness for surgery (min) | 7.2 (± 2.8) | 7.4 (± 3.2) | 5.1 (± 1.9) | 6.5 (± 2.8) |
| Trmb: Time to resolution of motor block (h) | 1.508 (± 0.423) | 1.488 (± 0.385) | 1.610 (± 0.429) | 1.538 (± 0.406) |
| Tua: Time to unassisted ambulation (h) | 2.744 (± 0.848) | 3.432 (± 1.191) | 3.252 (± 0.874) | 3.156 (± 1.000) |

| | | | | |
|---|---|---|---|---|
| TS1: Time to resolution of sensory block to S1 (h) | 1.813 (± 0.333) | 2.119 (± 0.394) | 2.218 (± 0.391) | 2.061 (± 0.404) |
| TSBmax: Time to maximum level of sensory block (mi | 0.224 (± 0.151) | 0.235 (± 0.082) | 0.241 (± 0.097) | 0.234 (± 0.110) |
| Trd: Time to regression of two dermatomers with re | 0.701 (± 0.392) | 0.840 (± 0.446) | 0.646 (± 0.228) | 0.727 (± 0.371) |
| Tuv: Time to first spontaneous urine voiding (h) | 2.579 (± 0.830) | 3.432 (± 1.191) | 3.096 (± 0.775) | 3.049 (± 0.987) |
| Tra: Time to administration of rescue anaesthesia | 0.800 (± 0.523) | 0.350 (± 0) | 0 (± 0) | 0.650 (± 0.452) |
| Tpa: Time to first post-operative analgesia (h) | 10.322 (± 11.841) | 3.091 (± 1.219) | 3.051 (± 1.220) | 5.580 (± 7.625) |
| Thd: Time to eligibility for home discharge (h) | 2.818 (± 0.786) | 3.523 (± 1.370) | 3.449 (± 0.861) | 3.279 (± 1.060) |

| | |
|---|---|
| **Attachments (see zip file)** | primary and secondary efficacy variables.PNG<br>p-values efficacy variables.PNG |

## Statistical analyses

| **Statistical analysis title** | comparison of time to events_overall comparison |
|---|---|

Statistical analysis description:

Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 2 v Dose 3 v Dose 1 |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | other[25] |
| P-value | = 0.1393 [26] |
| Method | Kruskal-wallis |

Notes:

[25] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[26] - p-value for Tsb
not statistically significant.
The p-values for the other parameters are listed in the picture attached in the previous page

| **Statistical analysis title** | comparison of time to events_D1 vs D3 |
|---|---|

Statistical analysis description:

Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 1 v Dose 3 |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other[27] |
| P-value | = 0.6917 [28] |
| Method | Wilcoxon rank-sum test |

Notes:

[27] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[28] - p-value for Tsb
not statistically significant.
The p-values for the other parameters are listed in the picture attached in the previous page

| **Statistical analysis title** | comparison of time to events_D2 vs D3 |
|---|---|

Statistical analysis description:

Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 3 v Dose 2 |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other[29] |
| P-value | = 0.0511 [30] |
| Method | Wilcoxon rank-sum test |

Notes:

[29] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[30] - p-value for Tsb
not statistically significant.
The p-values for the other parameters are listed in the picture attached in the previous page

| **Statistical analysis title** | comparison of time to events_D1 vs D2 |
|---|---|

Statistical analysis description:

Tsb, Tmb, Trs, TS1, Trmb, Tua, SBmax, TSBmax, Trd, Thd, Tuv, Tra and Tpa were summarised by dose level group and overall using descriptive statistics.
Due to the small sample size, collected data will be compared using nonparametric tests.
Above mentioned timings were analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 2 v Dose 1 |

| | |
|---|---|
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | other[31] |
| P-value | = 0.2446 [32] |
| Method | Wilcoxon rank-sum test |

Notes:

[31] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[32] - p-value for Tsb
not statistically significant.
The p-values for the other parameters are listed in the picture attached in the previous page

## Secondary: to assess the maximum level of sensory block_FAS

| | |
|---|---|
| End point title | to assess the maximum level of sensory block_FAS |

End point description:

To evaluate the maximum level of sensory block according to the following metameric level:
T2, T3, T4, T6, T7, T8, T10, T12 and L1

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

At visit 2/day 1

| End point values | Dose 1 | Dose 2 | Dose 3 | Full Analysis Set (FAS) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: number of patients | | | | |
| number (not applicable) | | | | |
| T2 | 0 | 2 | 2 | 4 |
| T3 | 1 | 0 | 1 | 2 |
| T4 | 3 | 2 | 1 | 6 |
| T6 | 0 | 1 | 4 | 5 |
| T7 | 1 | 0 | 1 | 2 |
| T8 | 3 | 3 | 2 | 8 |
| T10 | 3 | 1 | 3 | 7 |
| T12 | 3 | 5 | 1 | 9 |
| L1 | 1 | 1 | 0 | 2 |

| | |
|---|---|
| **Attachments (see zip file)** | max sensory block_FAS.PNG |

## Statistical analyses

| **Statistical analysis title** | comparison of SBmax_overall comparison |
|---|---|

Statistical analysis description:

The SBmax (maximum level of sensory block) was summarised by dose level group and overall using descriptive statistics. Due to the small sample size, collected data will be compared using nonparametric tests.
The overall comparison was analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| Comparison groups | Dose 1 v Dose 2 v Dose 3 |
|---|---|
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | other[33] |
| P-value | = 0.2591 [34] |
| Method | Kruskal-wallis |

Notes:

[33] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[34] - not statistically significant

| **Statistical analysis title** | comparison of SBmax_D1 vs D3 |
|---|---|

Statistical analysis description:

The SBmax (maximum level of sensory block) was summarised by dose level group and overall using descriptive statistics. Due to the small sample size, collected data will be compared using nonparametric tests.
The overall comparison was analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| Comparison groups | Dose 1 v Dose 3 |
|---|---|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[35] |
| P-value | = 0.1591 [36] |
| Method | Wilcoxon rank-sum test |

Notes:

[35] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[36] - not statistically significant

| **Statistical analysis title** | comparison of SBmax_D2 vs D3 |
|---|---|

Statistical analysis description:

The SBmax (maximum level of sensory block) was summarised by dose level group and overall using descriptive statistics. Due to the small sample size, collected data will be compared using nonparametric tests.
The overall comparison was analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 3 v Dose 2 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[37] |
| P-value | = 0.19 [38] |
| Method | Wilcoxon rank-sum test |

Notes:

[37] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[38] - not statistically significant

| **Statistical analysis title** | comparison of SBmax_D1 vs D2 |
|---|---|

Statistical analysis description:

The SBmax (maximum level of sensory block) was summarised by dose level group and overall using descriptive statistics. Due to the small sample size, collected data will be compared using nonparametric tests.
The overall comparison was analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test.

| | |
|---|---|
| Comparison groups | Dose 1 v Dose 2 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[39] |
| P-value | = 0.9333 [40] |
| Method | Wilcoxon rank-sum test |

Notes:

[39] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[40] - not statistically significant

## Secondary: to assess the maximum level of sensory block_PP

| End point title | to assess the maximum level of sensory block_PP |
|---|---|

End point description:

To evaluate the maximum level of sensory block according to the following metameric level:
T2, T3, T4, T6, T7, T8, T10, T12

| End point type | Secondary |
|---|---|

End point timeframe:

at V2/ day 1

| End point values | Dose 1 | Dose 2 | Dose 3 | Per Protocol set (PP) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 12 | 13 | 14 | 39 |
| Units: number of patients | | | | |
| number (not applicable) | | | | |
| T2 | 0 | 1 | 2 | 3 |
| T3 | 1 | 0 | 1 | 2 |
| T4 | 2 | 2 | 1 | 5 |
| T6 | 0 | 1 | 4 | 5 |
| T7 | 0 | 0 | 1 | 1 |
| T8 | 3 | 3 | 2 | 8 |
| T10 | 3 | 1 | 3 | 7 |
| T12 | 3 | 5 | 0 | 8 |

| Attachments (see zip file) | max sensory block_PP.PNG |
|---|---|

## Statistical analyses

| Statistical analysis title | comparison of SBmax_overall comparison |
|---|---|

Statistical analysis description:

The SBmax (maximum level of sensory block) was summarised by dose level group and overall using descriptive statistics. Due to the small sample size, collected data will be compared using nonparametric tests.
The overall comparison was analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test

| Comparison groups | Dose 3 v Dose 2 v Dose 1 |
|---|---|
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | other[41] |
| P-value | = 0.1118 [42] |
| Method | Kruskal-wallis |

Notes:

[41] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[42] - not statistically significant

| Statistical analysis title | comparison of SBmax_D1 vs D3 |
|---|---|

Statistical analysis description:

The SBmax (maximum level of sensory block) was summarised by dose level group and overall using descriptive statistics. Due to the small sample size, collected data will be compared using nonparametric tests.
The overall comparison was analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test

| Comparison groups | Dose 1 v Dose 3 |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other[43] |
| P-value | = 0.0843 [44] |
| Method | Wilcoxon rank-sum test |

Notes:

[43] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[44] - not statistically significant

| **Statistical analysis title** | comparison of SBmax_D2 vs D3 |
|---|---|

Statistical analysis description:

The SBmax (maximum level of sensory block) was summarised by dose level group and overall using descriptive statistics. Due to the small sample size, collected data will be compared using nonparametric tests.
The overall comparison was analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test

| | |
|---|---|
| Comparison groups | Dose 3 v Dose 2 |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other[45] |
| P-value | = 0.0975 [46] |
| Method | Wilcoxon rank-sum test |

Notes:

[45] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[46] - not statistically significant

| **Statistical analysis title** | comparison of SBmax_D1 vs D2 |
|---|---|

Statistical analysis description:

The SBmax (maximum level of sensory block) was summarised by dose level group and overall using descriptive statistics. Due to the small sample size, collected data will be compared using nonparametric tests.
The overall comparison was analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test

| | |
|---|---|
| Comparison groups | Dose 2 v Dose 1 |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | other[47] |
| P-value | = 0.9119 [48] |
| Method | Wilcoxon rank-sum test |

Notes:

[47] - Comparisons were performed according to the following hierarchical order:
1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison
Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary. However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

[48] - not statistically significant

## Secondary: to assess the effectiveness of anaesthesia_FAS

| End point title | to assess the effectiveness of anaesthesia_FAS |
|---|---|

End point description:

to evaluated the proportion of patients who have reached an effective anaesthesia with an adequacy of spinal block

| End point type | Secondary |
|---|---|

End point timeframe:

at V2/day 1

| End point values | Dose 1 | Dose 2 | Dose 3 | Full Analysis Set (FAS) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: number or patients | | | | |
| number (not applicable) | | | | |
| effective and adequate | 12 | 13 | 15 | 40 |
| ineffective and inadequate | 3 | 2 | 0 | 5 |

| Attachments (see zip file) | quality of spinal block_FAS.PNG<br>effectiveness of anaesthesia_FAS.PNG |
|---|---|

## Statistical analyses

No statistical analyses for this end point

## Secondary: to assess the effectiveness of anaesthesia_PP

| End point title | to assess the effectiveness of anaesthesia_PP |
|---|---|

End point description:

to evaluated the proportion of patients who have reached an effective anaesthesia with an adequacy of spinal block

| End point type | Secondary |
|---|---|

End point timeframe:

at V2/day 1

| End point values | Dose 1 | Dose 2 | Dose 3 | Per Protocol set (PP) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 12 | 13 | 14 | 39 |
| Units: number of patients | | | | |
| number (not applicable) | | | | |
| effective and adequate | 10 | 12 | 14 | 36 |
| ineffective and inadequate | 2 | 1 | 0 | 3 |

| Attachments (see zip file) | quality of spinal block_PP.PNG<br>effectiveness of anaesthesia_PP.PNG |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: To assess the concentration of chloroprocaine and its metabolite (CABA)

| End point title | To assess the concentration of chloroprocaine and its metabolite (CABA) |
|---|---|

End point description:

To assess the concentration of chloroprocaine and its metabolite 2-chloro-4-aminobenzoic acid (CABA) in plasma after administration of D1, D2 and D3.
NOTE:Chlorporocaine was below the quantification limit (4.0ng/ml) at all time points for all arms.
This is a pharmacokinetic variable

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Sampling times at day 1/ visit 2:
Pre-dose (0)_within 60 minutes before IMP administration
5, 10 min post dose_with no deviation admitted
30 min_+/- 1 minute post dose
60 min_+/- 3 minutes post dose

| End point values | Dose 1 | Dose 2 | Dose 3 | PK Set 1 (PK 1) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: ng/ml | | | | |
| geometric mean (standard deviation) | | | | |
| CABA_time 0 | 0 (± 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) |
| CABA_5 min | 16.127 (± 20.108) | 20.411 (± 23.037) | 24.887 (± 20.340) | 20.475 (± 21.030) |
| CABA_10 min | 41.440 (± 31.778) | 38.851 (± 25.492) | 75.833 (± 67.635) | 52.041 (± 47.689) |
| CABA_30 min | 57.459 (± 43.773) | 67.180 (± 36.899) | 97.647 (± 61.704) | 74.095 (± 50.538) |
| CABA_60 min | 47.020 (± 41.381) | 53.093 (± 31.803) | 78.380 (± 48.403) | 59.498 (± 42.435) |

| | |
|---|---|
| **Attachments (see zip file)** | CHL_CABA concentration_PK.pdf |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: To assess the excretion of the CABA in urine

| | |
|---|---|
| End point title | To assess the excretion of the CABA in urine |

End point description:

To assess the excretion of the CABA in urine (as % of the administered dose).
This is a pharmacokinetic variable

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:

at the time of first urine voiding at day 1/Visit 2 (day of surgery)

| **End point values** | Dose 1 | Dose 2 | Dose 3 | PK Set 2 (PK 2) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 14 | 14 | 43 |
| Units: % of administered dose | | | | |
| arithmetic mean (standard deviation) | 1.70085 (± 0.96883) | 1.75679 (± 0.93056) | 1.658058 (± 1.29205) | 1.70513 (± 1.04845) |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: To evaluate the incidence of treatment emergent adverse events (TEAEs) throughout the study

| | |
|---|---|
| End point title | To evaluate the incidence of treatment emergent adverse events (TEAEs) throughout the study |

End point description:

To investigate the safety and tolerability of the administered Chloroprocaine HCl 1% doses on the basis of treatment emergent adverse events (TEAEs) throughout the study.
This is a safety variable

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:

during the entire study period: from screening-visit 1 ( day -14 to day 1) to follow up visit (Day 7±1 ) post-surgery

| End point values | Dose 1 | Dose 2 | Dose 3 | Safety set |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: number of TEAEs | | | | |
| number (not applicable) | 0 | 0 | 0 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: to evaluate the incidence of transient neurological symptoms (TNS)

| End point title | to evaluate the incidence of transient neurological symptoms (TNS) |
|---|---|

End point description:

To investigate the safety and tolerability of the administered Chloroprocaine HCl 1% doses on the basis of transient neurological symptoms (TNS) at 24 h (day 2) and 6±1 days (day 7±1) after spinal puncture (Tsp).
This is a safety variable

| End point type | Other pre-specified |
|---|---|

End point timeframe:

at 24 h (day 2) and 6±1 days (day 7±1) after spinal puncture (Tsp)

| End point values | Dose 1 | Dose 2 | Dose 3 | Safety set |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: number of events | | | | |
| number (not applicable) | | | | |
| TNS_day 2_YES | 0 | 0 | 0 | 0 |
| TNS_day 2_NO | 15 | 15 | 15 | 45 |
| TNS_day 7±1_YES | 0 | 0 | 0 | 0 |
| TNS_day 7±1_NO | 15 | 15 | 15 | 45 |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: to collect blood pressure (BP) for safety assessment

| End point title | to collect blood pressure (BP) for safety assessment |
|---|---|

End point description:

The complete safety end point is to investigate the safety and tolerability of the administered

Chloroprocaine HCl 1% doses based on vital signs (blood pressure [BP], heart rate [HR] and peripheral oxygen saturation [SpO2]) check and ECG recording.
It was split in 4 sub-endpoints for entering values for each parameter
This is a safety variable

| End point type | Other pre-specified |
|---|---|

End point timeframe:

systolic and diastolic blood pressure at screening, baseline and discharge

| **End point values** | Dose 1 | Dose 2 | Dose 3 | Safety set |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic BP_screening | 120.0 (± 12.9) | 126.0 (± 21.4) | 121.6 (± 9.1) | 122.5 (± 15.2) |
| Systolic BP_baseline | 116.9 (± 10.5) | 127.9 (± 19.7) | 125.5 (± 14.1) | 123.4 (± 15.7) |
| Systolic BP_discharge | 116.9 (± 10.9) | 124.7 (± 14.7) | 121.7 (± 8.9) | 121.1 (± 11.9) |
| Diastolic BP_screening | 81.5 (± 12.1) | 78.9 (± 11.9) | 80.5 (± 9.9) | 80.3 (± 11.2) |
| Diastolic BP_baseline | 74.5 (± 10.3) | 79.8 (± 10.9) | 79.1 (± 13.3) | 77.8 (± 11.6) |
| Diastolic BP_discharge | 75.5 (± 12.2) | 79.0 (± 8.1) | 82.0 (± 9.5) | 78.8 (± 10.2) |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: To assess the pain at the injection site and at the surgery site at different timepoints

| End point title | To assess the pain at the injection site and at the surgery site at different timepoints |
|---|---|

End point description:

To investigate the safety and tolerability of the administered Chloroprocaine HCl 1% doses on the basis of pain assessment at the site of injection and at the site of surgery performed immediately after regression of spinal block, at discharge (final visit/ETV), 24 h (day 2) and 6±1 days (day 7±1) after spinal puncture.
This is a safety variable

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Pain assessment at these timepoints:
immediately after regression of spinal block
at discharge (final visit/ETV)
24 h (day 2) after spinal puncture
6±1 days (day 7±1) after spinal puncture

| **End point values** | Safety set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 45 | | | |
| Units: number of patients experienced pain | | | | |
| number (not applicable) | | | | |
| Pain injection site_after regression_0 | 45 | | | |
| Pain injection site_after regression_1 | 0 | | | |
| Pain injection site_after regression_2 | 0 | | | |
| Pain injection site_after regression_3 | 0 | | | |
| Pain injection site_after regression_4 | 0 | | | |
| Pain injection site_after regression_5 | 0 | | | |
| Pain injection site_after regression_6 | 0 | | | |
| Pain injection site_after regression_7 | 0 | | | |
| Pain injection site_after regression_8 | 0 | | | |
| Pain injection site_after regression_9 | 0 | | | |
| Pain injection site_after regression_10 | 0 | | | |
| Pain injection site_discharge_0 | 45 | | | |
| Pain injection site_discharge_1 | 0 | | | |
| Pain injection site_discharge_2 | 0 | | | |
| Pain injection site_discharge_3 | 0 | | | |
| Pain injection site_discharge_4 | 0 | | | |
| Pain injection site_discharge_5 | 0 | | | |
| Pain injection site_discharge_6 | 0 | | | |
| Pain injection site_discharge_7 | 0 | | | |
| Pain injection site_discharge_8 | 0 | | | |
| Pain injection site_discharge_9 | 0 | | | |
| Pain injection site_discharge_10 | 0 | | | |
| Pain injection site_day2_0 | 37 | | | |
| Pain injection site_day2_1 | 4 | | | |
| Pain injection site_day2_2 | 1 | | | |
| Pain injection site_day2_3 | 0 | | | |
| Pain injection site_day2_4 | 0 | | | |
| Pain injection site_day2_5 | 2 | | | |
| Pain injection site_day2_6 | 0 | | | |
| Pain injection site_day2_7 | 0 | | | |
| Pain injection site_day2_8 | 1 | | | |
| Pain injection site_day2_9 | 0 | | | |
| Pain injection site_day2_10 | 0 | | | |
| Pain injection site_day 7±1_0 | 44 | | | |
| Pain injection site_day 7±1_1 | 1 | | | |
| Pain injection site_day 7±1_2 | 0 | | | |
| Pain injection site_day 7±1_3 | 0 | | | |
| Pain injection site_day 7±1_4 | 0 | | | |
| Pain injection site_day 7±1_5 | 0 | | | |
| Pain injection site_day 7±1_6 | 0 | | | |
| Pain injection site_day 7±1_7 | 0 | | | |
| Pain injection site_day 7±1_8 | 0 | | | |
| Pain injection site_day 7±1_9 | 0 | | | |
| Pain injection site_day 7±1_10 | 0 | | | |
| Pain surgery site_after regression_0 | 13 | | | |
| Pain surgery site_after regression_1 | 2 | | | |

| | | | | |
|---|---|---|---|---|
| Pain surgery site_after regression_2 | 8 | | | |
| Pain surgery site_after regression_3 | 4 | | | |
| Pain surgery site_after regression_4 | 9 | | | |
| Pain surgery site_after regression_5 | 5 | | | |
| Pain surgery site_after regression_6 | 2 | | | |
| Pain surgery site_after regression_7 | 1 | | | |
| Pain surgery site_after regression_8 | 1 | | | |
| Pain surgery site_after regression_9 | 0 | | | |
| Pain surgery site_after regression_10 | 0 | | | |
| Pain surgery site_discharge_0 | 17 | | | |
| Pain surgery site_discharge_1 | 6 | | | |
| Pain surgery site_discharge_2 | 7 | | | |
| Pain surgery site_discharge_3 | 14 | | | |
| Pain surgery site_discharge_4 | 1 | | | |
| Pain surgery site_discharge_5 | 0 | | | |
| Pain surgery site_discharge_6 | 0 | | | |
| Pain surgery site_discharge_7 | 0 | | | |
| Pain surgery site_discharge_8 | 0 | | | |
| Pain surgery site_discharge_9 | 0 | | | |
| Pain surgery site_discharge_10 | 0 | | | |
| Pain surgery site_day2_0 | 20 | | | |
| Pain surgery site_day2_1 | 3 | | | |
| Pain surgery site_day2_2 | 6 | | | |
| Pain surgery site_day2_3 | 6 | | | |
| Pain surgery site_day2_4 | 3 | | | |
| Pain surgery site_day2_5 | 3 | | | |
| Pain surgery site_day2_6 | 2 | | | |
| Pain surgery site_day2_7 | 2 | | | |
| Pain surgery site_day2_8 | 0 | | | |
| Pain surgery site_day2_9 | 0 | | | |
| Pain surgery site_day2_10 | 0 | | | |
| Pain surgery site_day 7±1_0 | 37 | | | |
| Pain surgery site_day 7±1_1 | 3 | | | |
| Pain surgery site_day 7±1_2 | 0 | | | |
| Pain surgery site_day 7±1_3 | 3 | | | |
| Pain surgery site_day 7±1_4 | 0 | | | |
| Pain surgery site_day 7±1_5 | 2 | | | |
| Pain surgery site_day 7±1_6 | 0 | | | |
| Pain surgery site_day 7±1_7 | 0 | | | |
| Pain surgery site_day 7±1_8 | 0 | | | |
| Pain surgery site_day 7±1_9 | 0 | | | |
| Pain surgery site_day 7±1_10 | 0 | | | |

| | |
|---|---|
| **Attachments (see zip file)** | Pain assessment_Safety Set.pdf |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: to collect heart rate (HR) for safety assessment

| End point title | to collect heart rate (HR) for safety assessment |
|---|---|

End point description:

The complete safety end point is to investigate the safety and tolerability of the administered Chloroprocaine HCl 1% doses based on vital signs (blood pressure [BP], heart rate [HR] and peripheral oxygen saturation [SpO2]) check and ECG recording.
It was split in 4 sub-endpoints for entering values for each parameter
This is a safety variable

| End point type | Other pre-specified |
|---|---|

End point timeframe:

at screening, at baseline and at discharge

| End point values | Dose 1 | Dose 2 | Dose 3 | Safety set |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: beats/min | | | | |
| arithmetic mean (standard deviation) | | | | |
| HR_screening | 62.2 (± 8.5) | 67.5 (± 11.4) | 70.7 (± 8.6) | 66.8 (± 10.0) |
| HR_baseline | 63.1 (± 9.4) | 71.0 (± 14.0) | 71.7 (± 9.2) | 68.6 (± 11.5) |
| HR_discharge | 64.9 (± 7.0) | 66.9 (± 10.0) | 67.0 (± 8.0) | 66.2 (± 8.3) |

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: to collect peripheral oxygen saturation (SpO2) for safety assessment

| End point title | to collect peripheral oxygen saturation (SpO2) for safety assessment |
|---|---|

End point description:

The complete safety end point is to investigate the safety and tolerability of the administered Chloroprocaine HCl 1% doses based on vital signs (blood pressure [BP], heart rate [HR] and peripheral oxygen saturation [SpO2]) check and ECG recording.
It was split in 4 sub-endpoints for entering values for each parameter.
This is a safety variable.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

at screening, at baseline and at discharge

| End point values | Dose 1 | Dose 2 | Dose 3 | Safety set |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 45 |
| Units: HbO2/circulating Hb | | | | |
| arithmetic mean (standard deviation) | | | | |
| SpO2 (%)_screening | 99.07 (± 0.96) | 99.13 (± 1.25) | 98.53 (± 1.36) | 98.91 (± 1.20) |
| SpO2 (%)_baseline | 99.40 (± 0.91) | 99.13 (± 0.83) | 98.53 (± 1.51) | 99.02 (± 1.16) |
| SpO2 (%)_discharge | 99.33 (± 0.72) | 99.33 (± 0.90) | 99.00 (± 1.07) | 99.22 (± 0.90) |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

during the entire study period: from Visit 1 Days -14/1 to Follow up visit (Day 7±1)

Adverse event reporting additional description:

AEs were classified as pre-treatment AEs (PTAEs) and TEAEs according to the period of their occurrence, as follows:
- PTAEs: all AEs occurring before the IMP spinal injection and not worsening after the IMP spinal injection;
- TEAEs: all AEs occurring or worsening after the IMP spinal injection.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | CHL 30 mg |
| Reporting group description: | |
| subjects for safety set who received 30 mg of Chloroprocaine HCl 1% | |
| Reporting group title | CHL 40 mg |
| Reporting group description: | |
| subjects for safety set who received 40 mg of Chloroprocaine HCl 1% | |
| Reporting group title | CHL 50 mg |
| Reporting group description: | |
| subjects for safety set who received 50 mg of Chloroprocaine HCl 1% | |

| Serious adverse events | CHL 30 mg | CHL 40 mg | CHL 50 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 15 (0.00%) | 0 / 15 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | CHL 30 mg | CHL 40 mg | CHL 50 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 15 (100.00%) | 13 / 15 (86.67%) | 13 / 15 (86.67%) |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 15 (93.33%) | 13 / 15 (86.67%) | 13 / 15 (86.67%) |
| occurrences (all) | 15 | 13 | 13 |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 15 (6.67%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 3 / 15 (20.00%) | 3 / 15 (20.00%) |
| occurrences (all) | 2 | 3 | 3 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 15 (6.67%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 15 (6.67%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 15 (6.67%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

## 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

None reported