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 Units: Subjects			
Adults (18-64 years)	45	45	
From 65-84 years	0	0	
Age continuous Units: years			
arithmetic mean	40.6		
standard deviation	± 12.5	-	
Gender categorical 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 Units: Subjects			
Adults (18-64 years)	45	39	45
From 65-84 years	0	0	0
Age continuous Units: years			
arithmetic mean	40.6	41.3	40.6
standard deviation	± 12.6	± 12.5	± 12.6
Gender categorical 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 Units: Subjects			
Adults (18-64 years)	43	45	46
From 65-84 years	0	0	0
Age continuous Units: years			
arithmetic mean	40.7	40.6	40.6
standard deviation	± 12.9	± 12.6	± 12.5
Gender categorical 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 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 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 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