Clinical trial results:
A prospective, randomised, non-inferiority study of Chloroprocaine 2% and the active control Ropivacaine 0.75% (AstraZeneca) in ultrasound-guided axillary nerve block for short-duration distal upper limb surgery

Summary

EudraCT number	2014-002519-40
Trial protocol	AT
Global end of trial date	24 May 2017

Results information

Result version number	v1 (current)
This version publication date	18 September 2021
First version publication date	18 September 2021

Trial information

Trial identification

Sponsor protocol code	CHL.2/01-2014/M

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02385097
WHO universal trial number (UTN)	-
Other trial identifiers	Study protocol: CRO-14-120

Notes:

Sponsors

Sponsor organisation name	Sintetica SA
Sponsor organisation address	Via Penate 5, Mendrisio, Switzerland, 6850
Public contact	Study Management, CROSS SA, 0041 (0)916300510, corporate@croalliance.com
Scientific contact	Study Management, CROSS SA, 0041 (0)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	24 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluate the Non-inferiority evaluation of Test versus Reference product in terms of proportion of subjects with a successful block for distal upper limb surgeries, without any supplementation in the first 45 min (see definitions below), calculated from the time of readiness for surgery (complete sensory block).

Successful block: anaesthesia adequate for the surgery (complete sensory block), without any supplementation in the first 45 min (even if surgery lasts for > 45 min), calculated from the time of readiness for surgery (complete sensory block).
Supplementation: i.v. premedication or general anaesthesia or pre- or intra-operative systemic analgesia or additional local anaesthetic infiltration

Protection of trial subjects:

In order to avoid any risk for patients, the following exclusion criteria have been considered:
1.Physical findings: Clinically significant abnormal physical findings which could interfere with the objectives of the study. Contraindications to peripheral nerve block anaesthesia. History of neuromuscular diseases to the upper extremities
2.Axillary status: Axillary local infections, surgical scarring and pathological lymph node enlargement
3.ASA physical status: IV-V
4.Further anaesthesia: Patients anticipated to be requiring further anaesthesia (general or local anaesthesia)
5.Chronic pain syndromes: Patients with chronic pain syndromes (taking opioids, antidepressants, anticonvulsant agents)
6.Allergy: Ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients; ascertained or presumptive hypersensitivity to the amide and ester-type anaesthetics
7.Diseases: Significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that could interfere with the aim of the study; ascertained psychiatric diseases, sepsis, blood coagulation disorders, insulin dependent diabetes mellitus, terminal kidney failure
8.Medications: Medication known to interfere with the extent of regional blocks (see chloroprocaine and ropivacaine SmPCs) for 2 weeks before the start of the study. Hormonal contraceptives for females were allowed
9.Investigative drug studies: Participation in the evaluation of any investigational product for 3 months before this study, calculated from the first day of the month following the last visit of the previous study
10.Drug, alcohol: History of drug or alcohol abuse
11.Pregnancy: Missing or positive pregnancy test at screening, pregnant or lactating women

Background therapy:

N/A

Evidence for comparator:

Ropivacaine HCl 0.75% was chosen as the active control because it represents the gold standard anaesthetic for brachial plexus block procedures and it is commonly used in Germany, Switzerland and other European countries in brachial plexus block procedures.
Ropivacaine HCl 0.75% is the only authorised concentration of ropivacaine for this indication

Actual start date of recruitment	30 January 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	Switzerland: 87
Country: Number of subjects enrolled	Austria: 124
Worldwide total number of subjects	211
EEA total number of subjects	124

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)	147
From 65 to 84 years	60
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The recruitment lasted from April 2015 to May 2017 and occurred in Medical clinics and Hospitals

Pre-assignment

Screening details:

Inclusion criteria:
1.Male and female patients scheduled for short duration (< 60 min) distal upper limb surgery under axillary nerve block anaesthesia
2.Age ≥ 18 yo
3.BMI: 18-32 kg/m2 inclusive
4.ASA physical status: I-III
5.Signed ICF before inclusion in the study
6.Comprehension of the purpose of the study, including risks and side effects

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

All the clinical staff members involved in anaesthesia, surgery and study-related activities (Investigator/co-investigators/study nurses) as well as the patients were blind with respect to the administered treatment.
Syringes for injection were prepared out of the operating area by a person not involved in any other study-related activity. Only the person preparing the syringe and the CRA in charge of investigational products' accountability were aware of the administered treatments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Chloroprocaine

Arm description:

Chloroprocaine 2% Solution for injection, single administration by axillary nerve route 20 mL

Arm type	Experimental
Investigational medicinal product name	Chloroprocaine HCl 2%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:

Chloroprocaine HCl 2% injection (20 mg/mL)

Arm title	Ropivacaine

Arm description:

Naropin®, Ropivacaine 0.75% Solution for injection, single administration by axillary nerve route 20 mL

Arm type	Active comparator
Investigational medicinal product name	Ropivacaine HCl 0.75%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:

Naropin®, Ropivacaine HCl 0.75% injectable solution (7.5 mg/mL)

Number of subjects in period 1	Chloroprocaine	Ropivacaine
Started	106	105
Completed	105	103
Not completed	1	2
Consent withdrawn by subject	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	211	211	
Age categorical Units: Subjects			
Adults (18-64 years)	147	147	
From 65-84 years	60	60	
85 years and over	4	4	
Age continuous Units: years			
arithmetic mean	54.0		
standard deviation	± 17.1	-	
Gender categorical Units: Subjects			
Female	131	131	
Male	80	80	
Ethnic group Units: Subjects			
White	205	205	
Asian	4	4	
Other (Mestizo)	2	2	
Subject's Status Units: Subjects			
Inpatient	82	82	
Outpatient	129	129	

Subject analysis sets

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

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

Subject analysis set description:

all randomised patients who fulfilled the study protocol requirements in terms of study anaesthetics administration. This analysis set was used for sensitivity analyses and secondary efficacy analyses

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

Subject analysis set description:

All randomised patients who fulfilled 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 was used for the primary efficacy analysis and secondary efficacy analyses

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of the investigational medicinal product. This analysis set was used for the safety analyses

Reporting group values	Enrolled set	Full Analysis Set (FAS)	Per Protocol set (PP)
Number of subjects	211	209	197
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	54.0	54.1	54.0
standard deviation	± 17.1	± 17.2	± 17.4
Gender categorical Units: Subjects			
Female	131	129	123
Male	80	80	74
Ethnic group Units: Subjects			
White	205	203	192
Asian	4	4	3
Other (Mestizo)	2	2	2
Subject's Status Units: Subjects			
Inpatient	82	82	80
Outpatient	129	127	117

Reporting group values	Safety set		
Number of subjects	209		
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	54.1		
standard deviation	± 17.2		
Gender categorical Units: Subjects			
Female	129		
Male	80		
Ethnic group Units: Subjects			
White	203		
Asian	4		
Other (Mestizo)	2		

Subject's Status Units: Subjects			
Inpatient	82		
Outpatient	127		

End points

End points reporting groups

Reporting group title	Chloroprocaine
Reporting group description:	
Chloroprocaine 2% Solution for injection, single administration by axillary nerve route 20 mL	
Reporting group title	Ropivacaine
Reporting group description:	
Naropin®, Ropivacaine 0.75% Solution for injection, single administration by axillary nerve route 20 mL	
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	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
all randomised patients who fulfilled the study protocol requirements in terms of study anaesthetics administration. This analysis set was used for sensitivity analyses and secondary efficacy analyses	
Subject analysis set title	Per Protocol set (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomised patients who fulfilled 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 was used for the primary efficacy analysis and secondary efficacy analyses	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of the investigational medicinal product. This analysis set was used for the safety analyses	

Primary: Percentage of patients with successful block for distal upper limb surgeries_FAS

End point title	Percentage of patients with successful block for distal upper limb surgeries_FAS
End point description:	
Non-inferiority evaluation of Test versus Reference product in terms of proportion of patients with a successful block* for distal upper limb surgeries, without any supplementation** (i.e. no general anaesthesia or pre- and intra-operative systemic analgesia and no additional anaesthetic infiltration) in the first 45 min, calculated from the time of readiness for surgery (complete sensory block). *Successful block: anaesthesia adequate for the surgery (complete sensory block), without any supplementation in the first 45 min (even if surgery lasts for > 45 min), calculated from the time of readiness for surgery (complete sensory block). **Supplementation: i.v. premedication or general anaesthesia or pre- or intra-operative systemic analgesia or additional local anaesthetic infiltration.	
End point type	Primary
End point timeframe:	
at treatment-visit2, day 1 (day of surgery)	

End point values	Chloroprocaine	Ropivacaine	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	105	104	209	
Units: nr of patients				
pt who achieved a successful block	96	97	193	
pt who did not achieve a successful block	9	7	16	

Attachments (see zip file)	20180416-c120-csr_primary efficacy data.pdf

Statistical analyses

Statistical analysis title	proportion of subjects with a successful block FAS

Statistical analysis description:

The proportion of subjects (FAS set) who achieved a successful block, defined as anaesthesia adequate for the surgery, without any supplementation in the first 45 min from the time of readiness for surgery (see § 9.5.1.2), was 89/98 (90.8%) with Chloroprocaine HCl 2% and 92/99 (92.9%) with Ropivacaine HCl 0.75% (Table 14.2.1.1).

Comparison groups	Chloroprocaine v Ropivacaine
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0125
Method	binomial regression

Notes:

[1] - Results of the statistical analysis on the FAS (sensitivity analysis) confirmed the results obtained with the PP set (primary analysis), with 96/105 (91.4%) patients with a successful block for Chloroprocaine HCl 2% and 97/104 (93.3%) patients with a successful block for Ropivacaine HCl 0.75% (Table 14.2.1.2), and a derived 95% confidence interval of -0.091, 0039 (p-value=0.0125) (Table 14.2.1.5).

Primary: Percentage of patients with successful block for distal upper limb surgeries _PP

End point title	Percentage of patients with successful block for distal upper limb surgeries _PP

End point description:

Non-inferiority evaluation of Test versus Reference product in terms of proportion of patients with a successful block* for distal upper limb surgeries, without any supplementation** (i.e. no general anaesthesia or pre- and intra-operative systemic analgesia and no additional anaesthetic infiltration) in the first 45 min, calculated from the time of readiness for surgery (complete sensory block).
*Successful block: anaesthesia adequate for the surgery (complete sensory block), without any supplementation in the first 45 min (even if surgery lasts for > 45 min), calculated from the time of readiness for surgery (complete sensory block).
**Supplementation: i.v. premedication or general anaesthesia or pre- or intra-operative systemic analgesia or additional local anaesthetic infiltration.

End point type	Primary

End point timeframe:

at treatment-visit 2/ day 1 (day of surgery)

End point values	Chloroprocaine	Ropivacaine	Per Protocol set (PP)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	98	99	197	
Units: nr of patients				
pt who achived successful block	89	92	181	
pt who did not achive successful block	9	7	16	

Attachments (see zip file)	20180416-c120-csr_primary efficacy data.pdf

Statistical analyses

Statistical analysis title	frequency of patients with a successful block PP

Statistical analysis description:

The proportion of subjects (PP set) who achieved a successful block, defined as anaesthesia adequate for the surgery, without any supplementation in the first 45 min from the time of readiness for surgery (see § 9.5.1.2), was 89/98 (90.8%) with Chloroprocaine HCl 2% and 92/99 (92.9%) with Ropivacaine HCl 0.75% (Table 14.2.1.1).

Comparison groups	Ropivacaine v Chloroprocaine
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.021
Method	binomial regression

Notes:

[2] - The overall proportion of subjects with a successful block (all centres) was compared between treatment groups using a binomial regression model, with the factors treatment and analysis centre as fixed effects. Results showed that non-inferiority of Chloroprocaine HCl 2% with respect to Ropivacaine HCl 0.75%, administered by axillary injection under ultrasound guidance, was confirmed (Table 14.2.1.3).

Secondary: Time to onset of sensory block_PP

End point title	Time to onset of sensory block_PP

End point description:

Time period from completion of the final perineural injection (time 0 h) to achievement of sensory block in the 4 nerve territories

End point type	Secondary

End point timeframe:

at treatment-visit 2/day 1 (day of surgery), up to 1 h after last perineural injection

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[3]	99[4]		
Units: minute				
median (confidence interval 95%)	10.0 (10.0 to 15.0)	15.0 (10.0 to 15.0)		

Notes:

[3] - Nr of subjects with event:96
Nr of censored subjects: 2
[4] - Nr of subjects with event:95
Nr of censored subjects: 4

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of sensory block_FAS

End point title	Time to onset of sensory block_FAS

End point description:

Time period from completion of the final perineural injection (time 0 h) to achievement of sensory block in the 4 nerve territories

End point type	Secondary

End point timeframe:

at treatment-visit 2/day 1 (day of surgery), up to 1 h after last perineural injection

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[5]	104[6]		
Units: minute				
median (confidence interval 95%)	10.0 (10.0 to 15.0)	15.0 (10.0 to 15.0)		

Notes:

[5] - Nr of subjects with event:103
Nr of censored subjects: 2
[6] - Nr of subjects with event:100
Nr of censored subjects: 4

Statistical analyses

Statistical analysis title	aa
Comparison groups	Ropivacaine v Chloroprocaine
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0896
Method	Logrank

Secondary: Time to Onset of Motor Block _PP

End point title	Time to Onset of Motor Block _PP

End point description:

Time period from completion of the final perineural injection (time 0 h) to achievement of motor block

End point type	Secondary

End point timeframe:

at treatment-visit 2/day 1 /day of surgery), up to 1 h after last perineural injection

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[7]	99[8]		
Units: minute				
median (confidence interval 95%)	10.0 (5.0 to 10.0)	10.0 (5.0 to 10.0)		

Notes:

[7] - Nr of subjects with event:98
Nr of censored subjects: 0
[8] - Nr of subjects with event:96
Nr of censored subjects: 3

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Motor Block _FAS

End point title	Time to Onset of Motor Block _FAS

End point description:

Time period from completion of the final perineural injection (time 0 h) to achievement of motor block

End point type	Secondary

End point timeframe:

at treatment-visit 2/day 1 /day of surgery), up to 1 h after last perineural injection

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[9]	104[10]		
Units: minute				
median (confidence interval 95%)	10.0 (5.0 to 10.0)	10.0 (5.0 to 10.0)		

Notes:

[9] - Nr of subjects with event:105
Nr of censored subjects: 0
[10] - Nr of subjects with event:101
Nr of censored subjects: 3

Statistical analyses

No statistical analyses for this end point

Secondary: Time to regression of sensory block_FAS

End point title	Time to regression of sensory block_FAS

End point description:

Was deemed to have occurred when cold sensation and sensitive perception had returned (if assessable) in at least one nerve territory.

End point type	Secondary

End point timeframe:

at treatment-visit 2/day 1, up to 12 hrs after surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[11]	104[12]		
Units: minute				
median (confidence interval 95%)	68.0 (64.0 to 75.0)	451.0 (413.0 to 480.0)		

Notes:

[11] - Nr of subjects with event:105
Nr of censored subjects: 0
[12] - Nr of subjects with event:95
Nr of censored subjects: 9

Statistical analyses

No statistical analyses for this end point

Secondary: Time to regression of sensory block_PP

End point title	Time to regression of sensory block_PP

End point description:

Was deemed to have occurred when cold sensation and sensitive perception had returned (if assessable) in at least one nerve territory.

End point type	Secondary

End point timeframe:

at treatment-visit 2/day 1, up to 12 hrs after surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[13]	99[14]		
Units: minute				
median (confidence interval 95%)	69.5 (65.0 to 75.0)	444.0 (413.0 to 475.0)		

Notes:

[13] - Nr of subjects with event:98
Nr of censored subjects: 0
[14] - Nr of subjects with event:91
Nr of censored subjects: 8

Statistical analyses

No statistical analyses for this end point

Secondary: Time to regression of motor block_PP

End point title	Time to regression of motor block_PP

End point description:

Was deemed to have occurred when motor score was ≥ 3 in at least one nerve territory.

End point type	Secondary

End point timeframe:

at treatment-visit 2/day 1, up to 12 hrs after surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[15]	99[16]		
Units: minute				
median (confidence interval 95%)	65.0 (63.0 to 69.0)	405.0 (384.0 to 460.0)		

Notes:

[15] - Nr of subjects with event:98
Nr of censored subjects: 0
[16] - Nr of subjects with event:89
Nr of censored subjects: 10

Statistical analyses

No statistical analyses for this end point

Secondary: Time to regression of motor block_FAS

End point title	Time to regression of motor block_FAS

End point description:

Was deemed to have occurred when motor score was ≥ 3 in at least one nerve territory.

End point type	Secondary

End point timeframe:

at treatment-visit 2/day 1, up to 12 hrs after surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[17]	104[18]		
Units: minute				
median (confidence interval 95%)	65.0 (60.0 to 69.0)	415.0 (388.0 to 460.0)		

Notes:

[17] - Nr of subjects with event:105
Nr of censored subjects: 0
[18] - Nr of subjects with event:92
Nr of censored subjects: 12

Statistical analyses

No statistical analyses for this end point

Secondary: Time to administration of rescue anaesthesia or rescue analgesia_PP

End point title	Time to administration of rescue anaesthesia or rescue analgesia_PP

End point description:

Time from completion of the final perineural injection (time 0 h) to administration of the first rescue anaesthesia or analgesia (supplementation) (if applicable)

NOTE: 0 was entered as results. According to the CSR, NC (not calculated) was the correct answer, not possible to enter.

End point type	Secondary

End point timeframe:

45 min from the time of readiness of surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[19]	99[20]		
Units: hour				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Notes:

[19] - Nr of subjects with event:9
Nr of censored subjects: 89
[20] - Nr of subjects with event:7
Nr of censored subjects: 92

Statistical analyses

No statistical analyses for this end point

Secondary: Time to administration of rescue anaesthesia or rescue analgesia_FAS

End point title	Time to administration of rescue anaesthesia or rescue analgesia_FAS

End point description:

Time from completion of the final perineural injection (time 0 h) to administration of the first rescue anaesthesia or analgesia (supplementation) (if applicable)
NOTE: 0 was entered as results. According to the CSR, NC (not calculated) was the correct answer, not possible to enter.

End point type	Secondary

End point timeframe:

45 min from the time of readiness of surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[21]	104[22]		
Units: hour				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Notes:

[21] - Nr of subjects with event:9
Nr of censored subjects: 96
[22] - Nr of subjects with event:7
Nr of censored subjects: 97

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first post-operative analgesia_PP

End point title	Time to first post-operative analgesia_PP

End point description:

Time from completion of the final perineural injection (time 0 h) to the first post-operative analgesia.
NOTE:
For Chloroprocaine: Lower limit of the confidence interval was 200.0, upper was NC (not calculated). For avoiding error, 0 (zero) was entered for both.
For Ropivacaine: Lower limit of the confidence interval was 783.0, upper was NC (not calculated). For avoiding error, 0 (zero) was entered for both

End point type	Secondary

End point timeframe:

From surgery day to 24 hrs post surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[23]	99[24]		
Units: minute				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Notes:

[23] - Nr of subjects with event: 48
Nr of censured subjects: 50

[24] - Nr of subjects with event: 45
Nr of censured subjects: 54

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first post-operative analgesia_FAS

End point title	Time to first post-operative analgesia_FAS

End point description:

Time from completion of the final perineural injection (time 0 h) to the first post-operative analgesia
NOTE:
For Chloroprocaine: Lower limit of the confidence interval was 205.0, upper was NC (not calculated). For avoiding error, 0 (zero) was entered for both.
For Ropivacaine: Lower limit of the confidence interval was 822.0, upper was NC (not calculated). For avoiding error, 0 (zero) was entered for both

End point type	Secondary

End point timeframe:

From surgery day to 24 hrs post surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[25]	104[26]		
Units: minute				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Notes:

[25] - Nr of subjects with event:49
Nr of censored subjects: 56

[26] - Nr of subjects with event:46
Nr of censored subjects: 58

Statistical analyses

No statistical analyses for this end point

Secondary: Time to eligibility for home discharge_PP

End point title	Time to eligibility for home discharge_PP

End point description:

Time from completion of the final perineural injection (time 0 h) to the time when the criteria for discharge were met, even if, according to the hospital procedures, the patient was discharged from the hospital at a later time

End point type	Secondary

End point timeframe:

from surgery day to 24h post surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[27]	99[28]		
Units: minute				
median (confidence interval 95%)	164.0 (155.0 to 171.0)	380.0 (209.0 to 450.0)		

Notes:

[27] - Nr of subjects with event:98
Nr of censored subjects: 0
[28] - Nr of subjects with event:99
Nr of censored subjects: 0

Statistical analyses

No statistical analyses for this end point

Secondary: Time to eligibility for home discharge_FAS

End point title	Time to eligibility for home discharge_FAS

End point description:

Time from completion of the final perineural injection (time 0 h) to the time when the criteria for discharge were met, even if, according to the hospital procedures, the patient was discharged from the hospital at a later time

End point type	Secondary

End point timeframe:

from surgery day to 24h post surgery

End point values	Chloroprocaine	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[29]	104[30]		
Units: minute				
median (confidence interval 95%)	161.0 (155.0 to 170.0)	355.5 (206.0 to 450.0)		

Notes:

[29] - Nr of subjects with event:105
Nr of censored subjects: 0
[30] - Nr of subjects with event:104
Nr of censored subjects: 0

Statistical analyses

No statistical analyses for this end point

Secondary: global incidence of treatment-emergent adverse events (TEAEs)

End point title	global incidence of treatment-emergent adverse events (TEAEs)

End point description:

Number of Treatment-emergent Adverse Events (TEAEs) occurring or worsening after the first dose of IMP

End point type	Secondary

End point timeframe:

from surgery day to day 6 +/- 1 after surgery

End point values	Chloroprocaine	Ropivacaine	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	105	105	209	
Units: number of event				
number (not applicable)				
total nr of TEAEs	115	153	268	
related	0	12	12	
not related	115	141	256	
mild	68	92	160	
moderate	46	46	92	
severe	1	15	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of neurological symptoms

End point title	Incidence of neurological symptoms

End point description:

Number of patients with Neurological Symptoms (e.g. paraesthesia, motor function problems and pain at the injection site)
Following syntomps have been investigated:
Burning

Tingling
Pins and needles sensation (for category title, summarized as "pins sensation")
Pricking
Aching
Numbness
Hypoesthesia
Pain surgery site
At Day 7±1, pain at surgery site was not evaluated and diffuse hair loss, headache and Itching were evaluated.

End point type	Secondary

End point timeframe:

from surgery day to day 6 +/- 1 after surgery

End point values	Chloroprocaine	Ropivacaine	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	105	104	209	
Units: nr of patients				
number (not applicable)				
Discharge_Burning_Mild	4	1	5	
Discharge_Burning_Moderate	4	0	4	
Discharge_Burning_Severe	0	0	0	
Discharge_Burning_Tot	8	1	9	
Discharge_Tingling_Mild	4	9	13	
Discharge_Tingling_Moderate	5	15	20	
Discharge_Tingling_Severe	0	2	2	
Discharge_Tingling_Tot	8	25	33	
Discharge_pins sensation_Mild	1	4	5	
Discharge_pins sensation_Moderate	0	1	1	
Discharge_pins sensation_Severe	0	0	0	
Discharge_pins sensation_Tot	1	5	6	
Discharge_Pricking_Mild	5	3	8	
Discharge_Pricking_Moderate	3	1	4	
Discharge_Pricking_Severe	0	1	1	
Discharge_Pricking_Tot	8	5	13	
Discharge_Aching_Mild	7	4	11	
Discharge_Aching_Moderate	4	1	5	
Discharge_Aching_Severe	0	1	1	
Discharge_Aching_Tot	10	6	16	
Discharge_Numbness_Mild	1	6	7	
Discharge_Numbness_Moderate	1	12	13	
Discharge_Numbness_Severe	0	9	9	
Discharge_Numbness_Tot	2	27	29	
Discharge_Hypoesthesia_Mild	4	8	12	
Discharge_Hypoesthesia_Moderate	1	5	6	
Discharge_Hypoesthesia_Severe	0	1	1	
Discharge_Hypoesthesia_Totale	5	14	19	
Discharge_Pain surgery site_Mild	0	1	1	
Discharge_Pain surgery site_Moderate	0	0	0	
Discharge_Pain surgery site_Severe	0	0	0	
Discharge_Pain surgery site_Tot	0	1	1	
Day 7±1_Burning_mild	5	3	8	

Day 7±1_Burning_moderate	1	1	2	
Day 7±1_Burning_severe	0	0	0	
Day 7±1_Burning_tot	6	4	10	
Day 7±1_Tingling_mild	5	5	10	
Day 7±1_Tingling_moderate	0	2	2	
Day 7±1_Tingling_severe	0	0	0	
Day 7±1_Tingling_tot	5	6	11	
Day 7±1_pins sensation_mild	1	0	1	
Day 7±1_pins sensation_moderate	1	0	1	
Day 7±1_pins sensation_severe	0	0	0	
Day 7±1_pins sensation_tot	2	0	2	
Day 7±1_Pricking_mild	2	4	6	
Day 7±1_Pricking_moderate	0	0	0	
Day 7±1_Pricking_severe	0	0	0	
Day 7±1_Pricking_tot	2	4	6	
Day 7±1_Aching_mild	3	3	6	
Day 7±1_Aching_moderate	1	0	1	
Day 7±1_Aching_severe	0	0	0	
Day 7±1_Aching_tot	4	3	7	
Day 7±1_Numbness_mild	1	2	3	
Day 7±1_Numbness_moderate	1	1	2	
Day 7±1_Numbness_severe	0	0	0	
Day 7±1_Numbness_tot	2	3	5	
Day 7±1_Hypoesthesia_mild	5	5	10	
Day 7±1_Hypoesthesia_moderate	0	0	0	
Day 7±1_Hypoesthesia_severe	0	0	0	
Day 7±1_Hypoesthesia_tot	5	5	10	
Day 7±1_diffuse hair loss_mild	0	0	0	
Day 7±1_diffuse hair loss_moderate	0	0	0	
Day 7±1_diffuse hair loss_severe	0	1	1	
Day 7±1_diffuse hair loss_tot	0	1	1	
Day 7±1_headache_mild	1	0	1	
Day 7±1_headache_moderate	0	0	0	
Day 7±1_headache_severe	1	0	1	
Day 7±1_headache_tot	2	0	2	
Day 7±1_Itching_mild	0	0	0	
Day 7±1_Itching_moderate	0	1	1	
Day 7±1_Itching_severe	0	0	0	
Day 7±1_Itching_tot	0	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Heart rate (HR)

End point title	Heart rate (HR)

End point description:

for safety assessment
The following normal ranges Heart Rate parameters will be used:
50-90 beats/min

End point type	Secondary

End point timeframe:

from surgery day to 24 hrs post surgery

End point values	Chloroprocaine	Ropivacaine	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	105	104	209	
Units: beats/minute				
median (confidence interval 95%)				
screening	72.0 (50 to 110)	72.0 (50 to 99)	72.0 (50 to 110)	
baseline	72.0 (51 to 102)	70.0 (45 to 104)	71.0 (45 to 104)	
discharge	70.0 (46 to 99)	72.0 (47 to 100)	71.0 (46 to 100)	

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Pressure (BP)

End point title	Blood Pressure (BP)

End point description:

for safety assessment.
The following normal ranges Systolic and Diastolic Blood Pressure parameters will be used:
Systolic Blood Pressure: 100-139 mmHg Diastolic Blood Pressure: 50-89 mmHg

End point type	Secondary

End point timeframe:

from surgery day to 24 hrs post surgery

End point values	Chloroprocaine	Ropivacaine	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	105	104	209	
Units: mmHg				
median (confidence interval 95%)				
Systolic BP at screening	136.0 (88 to 200)	132.0 (105 to 182)	132.0 (88 to 200)	
Systolic BP at baseline	135.0 (98 to 187)	137.5 (106 to 194)	135.0 (98 to 194)	
Systolic BP at discharge	130.0 (90 to 185)	129.0 (90 to 186)	129.0 (90 to 186)	
Diastolic BP at screening	80.0 (43 to 110)	80.0 (50 to 104)	80.0 (43 to 110)	
Diastolic BP at baseline	78.0 (54 to 120)	80.0 (60 to 113)	80.0 (54 to 120)	
Diastolic BP at discharge	74.0 (50 to 99)	75.0 (50 to 99)	75.0 (50 to 99)	

Statistical analyses

No statistical analyses for this end point

Secondary: peripheral oxygen saturation (SpO2)

End point title	peripheral oxygen saturation (SpO2)

End point description:

for safety assessment.
The following normal ranges SpO2 parameters will be used:
Peripheral Oxygen Saturation: ≥ 95%

End point type	Secondary

End point timeframe:

from surgery day to 24 hrs post surgery

End point values	Chloroprocaine	Ropivacaine	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	105	104	209	
Units: percent				
median (confidence interval 95%)				
baseline	97.00 (92.0 to 100.0)	97.00 (90.0 to 100.0)	97.00 (90.0 to 100.0)	
discharge	98.00 (94.0 to 100.0)	98.00 (94.0 to 100.0)	98.00 (94.0 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from Visit 1 - Screening to Telephonic Follow-up (from Days -14/1 to Day 7±1)

Adverse event reporting additional description:

AEs monitored from the screening visit, immediately after informed consent signature, up to the telephonic follow-up. Particular attention was given to systemic and local toxicity symptoms, neurological symptoms (e.g. paraesthesia, motor function problems and pain at the injection site) and allergic reactions.

NO SAE occurred.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Chloroprocaine
Reporting group description: -	
Reporting group title	Ropivacaine
Reporting group description: -	
Reporting group title	Safety Set

Reporting group description: -

Serious adverse events	Chloroprocaine	Ropivacaine	Safety Set
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 105 (0.00%)	0 / 104 (0.00%)	0 / 209 (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	Chloroprocaine	Ropivacaine	Safety Set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 105 (55.24%)	76 / 104 (73.08%)	134 / 209 (64.11%)
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	48 / 105 (45.71%)	41 / 104 (39.42%)	89 / 209 (42.58%)
occurrences (all)	50	43	93
Vascular disorders			

Hypotension			
subjects affected / exposed	0 / 105 (0.00%)	1 / 104 (0.96%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	9 / 105 (8.57%)	38 / 104 (36.54%)	47 / 209 (22.49%)
occurrences (all)	10	44	54
Paraesthesia			
subjects affected / exposed	17 / 105 (16.19%)	28 / 104 (26.92%)	45 / 209 (21.53%)
occurrences (all)	22	40	62
Burning sensation			
subjects affected / exposed	11 / 105 (10.48%)	5 / 104 (4.81%)	16 / 209 (7.66%)
occurrences (all)	11	5	16
Headache			
subjects affected / exposed	3 / 105 (2.86%)	1 / 104 (0.96%)	4 / 209 (1.91%)
occurrences (all)	3	1	4
Sensorimotor disorder			
subjects affected / exposed	0 / 105 (0.00%)	1 / 104 (0.96%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	6 / 105 (5.71%)	5 / 104 (4.81%)	11 / 209 (5.26%)
occurrences (all)	6	5	11
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 105 (0.95%)	4 / 104 (3.85%)	5 / 209 (2.39%)
occurrences (all)	1	4	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 104 (0.96%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Erythema			
subjects affected / exposed	0 / 105 (0.00%)	1 / 104 (0.96%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Pruritus			

subjects affected / exposed	0 / 105 (0.00%)	1 / 104 (0.96%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	11 / 105 (10.48%)	6 / 104 (5.77%)	17 / 209 (8.13%)
occurrences (all)	12	6	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2014	Amendment 1.0, final protocol version 2.0 dated 17SEP2014. The following points have been added: Inclusion in the study of inpatients beside outpatients Urine pregnancy test for women at screening visit An impartial witness can sign the informed consent form when the subject is physically unable to sign due to the distal upper limb injury Normal ranges for haemodynamic variables and ECG Recommended maximal deviations from the scheduled block assessment times. The secondary study variable "time to home discharge" has been changed into "time to eligibility for home discharge" A typing mistake at § 8.2 has been corrected An address at § 16.4 has been changed A reference at § 17 has been changed
18 December 2014	Amendament 2.0, final protocol version 3.0 dated 3DEC2014. The following changes have been introduced: The study will be performed as double blind and not as observer-blind Assessment of neurological symptoms as safety secondary endpoint Clinical justification of the chosen non-inferiority limit Clinical justification of the expected success rate in both treatment arms Conditions that will be used for establishing the convergence failure of the binomial regression model and, consequently, for applying the Poisson regression model with a robust error variance A mistake in the exclusion criteria n. 6 has been corrected. Discharge criteria based on the modified Aldrete's scale have been corrected. The e-mail address for SAE reporting has been changed. The name of one of the companies in charge of the study monitoring has changed In § 13.1 a sentence has been added. Some additional minor changes have been introduced.
30 July 2015	Amendment Nr. 4, protocol final version 4.0 dated 22MAY2015 The present amendment introduces the following changes in the study protocol: -A new Clinical Site has been involved in the study to replace the German site of Marburg, following the negative opinion of the Ethics Committee of the Faculty of Medicine of Marburg, which rejected the study on the basis of statistical considerations about the non-inferiority margin. On the contrary, the German Regulatory Authority BfArM approved the study without any concern. In Switzerland the study was approved by the Cantonal Ethics Committee of Ticino and by the Regulatory Authority Swissmedic. -Prof. Hinnerk Wulf, MD. Professor and Chairman of the Department of Anesthesiology and Intensive Care Medicine of the University Hospital of Marburg is now Medical Adviser -One of the companies in charge of the study monitoring has changed -The sample size of the study has been recalculated using a higher power (85% instead of 80%) -It has been further clarified that the reference time for calculating the scheduled time interval of the post-surgery assessments is the time of surgery end

10 November 2015	Amendment 5, final protocol version 5.0 dated 9OCT2015 The present amendment introduces the following changes in the study protocol: - A second Clinical Site in Austria (clinical centre N. 4) has been involved in the study - The Swiss Site of Bellinzona (clinical centre N. 3) has terminated its participation in the study due to enrolment difficulties - Prof. Oliver Kimberger, Medical Director of Orthopedic and Trauma Anesthesia, Department of General Anesthesia and Intensive Care Medicine of the Medical University of Vienna (clinical centre N. 1), is now the coordinating investigator in Austria - The definitions of sensory and motor block regression have been clarified - The definition of analysis centres has been introduced The rationale for the change is the need to replace the Swiss site of Bellinzona following its withdrawal from the study due to difficulties with patients' recruitment and to introduce the definition of analysis centres for the study statistical analysis. This amendment is considered substantial because it introduces a new Clinical Site and the definition of the analysis centres, which will be used as fixed effect in the regression model of the primary efficacy analysis instead of the clinical centres.
28 December 2016	Amendment 7 dated 13DEC2016. The present amendment introduces the following changes to the study protocol: -Clinical site N. 4 (Klagenfurt, Austria. Principal Investigator: Prof. R. Likar) will enrol 36 and not 60 patients as previously planned. The 24 patients not enrolled at this site will be redistributed. These patients will be enrolled at site N. 1 (16 patients) and N.2 (8 patients), as also detailed below. -Clinical site N. 1 (Vienna, Austria. Principal Investigator: Prof. O. Kimberger) will enrol 16 additional patients for a total of 88 patients (72 patients as originally planned + 16 additional patients) -Clinical site N. 2 (Gravesano, Switzerland. Principal Investigator: Dr. C. Camponovo) will enrol 8 additional patients for a total of 80 patients (72 patients as originally planned + 8 additional patients) -The reason for exclusion from the Per Protocol set "more than 20% of the actual block assessment times outside the recommended ranges" has to be changed into "deviations from the actual block assessment times until readiness for surgery outside the recommended ranges that can bias the evaluation of the time of readiness for surgery"

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported