Study CRO-14-120 - Sponsor code CHL.2/01-2014/M

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

Prospective, randomised, multi-centre, active-controlled, observer-blind, parallel-group, non-inferiority study

EudraCT Number: 2014-002519-40

Test product:	Chloroprocaine HCl 2% injection (20 mg/mL), Sintetica S.A., Switzerland
Reference product:	Naropin®, Ropivacaine HCl 0.75% injectable solution (7.5 mg/mL), AstraZeneca GmbH, Germany
Sponsor:	Sintetica S.A., Via Penate 5, CH-6850 Mendrisio, Switzerland Phone: +41.91.640.42.50; Fax: +41.91.646.85.61
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Development phase:	Phase III
Version and date:	Final version 2.0, 17SEP14

This study will be conducted in accordance with Good Clinical Practice (GCP), ICH topic E6

This document comprises 67 pages

VERSIONS' HISTORY

Version	Date	Description of Changes
1.0	18 June 2014	Original document
2.0	17 Sep 2014	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. In these cases, the witness should sign and personally date the consent form after the subject has orally consented to the participation in the trial and, if capable of signing, has signed and personally dated the informed consent form ➢ 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

PROTOCOL APPROVAL

SPONSOR
Sintetica S.A., Switzerland

Clinical Project Leader
Elisabetta Donati, Corporate Director Scientific Affairs

Date	Signature

PRINCIPAL INVESTIGATORS

I have read this protocol and agree to conduct this study in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki.

Principal investigator – Centre N. 1 - Germany
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Date	Signature

I have read this protocol and agree to conduct this study in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki.

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Date	Signature

I have read this protocol and agree to conduct this study in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki.

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Department of Anaesthesiology, Ospedale Regionale di Bellinzona e Valli-Bellinzona, Bellinzona, Switzerland

Date	Signature

CRO
CROSS S.A., Switzerland, and its affiliated companies CROSS Research S.A. and CROSS Metrics S.A.

Coordination
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Chiara Leuratti, Medical Writing Manager, Unit Head

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Matteo Rossini, Biometry Manager, Unit Head

Date _____ Signature _____

Quality Assurance Unit Representative
Mario Corrado, Quality Assurance Manager, Unit Head

Date _____ Signature _____

STUDY SYNOPSIS

Name of Investigational Product: Chloroprocaine HCl 2% injection
Name of Active Ingredient: Chloroprocaine
Indication: Local anaesthesia by axillary nerve block
Title of Study: 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
Protocol Sponsor code: CHL.2/01-2014/M
Clinical phase: Phase III
Trial design: Prospective, randomised, multi-centre, active-controlled, observer-blind, parallel-group, non-inferiority study
Planned n. of centres / countries: Three centres / Germany and Switzerland
Investigators and centres: 1) *Centre N. 1* - Principal investigator: Prof. Hinnerk Wulf, MD. Professor and Chairman, Department of Anesthesiology and Intensive Care Medicine, University Hospital, D-35033 Marburg, Germany 2) *Centre N. 2* - Principal investigator: Claudio Camponovo MD. Chairman, Department of Anaesthesiology, Clinica Ars Medica, Via Cantonale, CH-6929 Gravesano, Switzerland 3) *Centre N. 3* - Principal investigator: Andrea Saporito, MD MHA. Chairman, Department of Anaesthesiology Ospedale Regionale di Bellinzona e Valli-Bellinzona, CH-6500 Bellinzona, Switzerland
Test investigational medicinal product (IMP) – dose and mode of administration: Chloroprocaine HCl 2% Injection (20 mg/mL), injectable solution, Sintetica S.A., Switzerland. Total dose = 20 mL (400 mg), approximately 5 mL (100 mg) per nerve. The mode of administration is detailed below (*Study procedures, Procedure for ultrasound-guided axillary block*).
Reference IMP, dosage and mode of administration: Naropin®, Ropivacaine HCl 0.75% (7.5 mg/mL) injectable solution, AstraZeneca GmbH, Germany. Total dose = 20 mL (150 mg), approximately 5 mL (37.5 mg) per nerve. The mode of administration is detailed below (*Study procedures, Procedure for ultrasound-guided axillary block*).
OBJECTIVES: **Primary objective:** 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). **Secondary objectives:** Comparison between Test and Reference products in terms of the time to onset of sensory block [time to readiness for surgery], time to regression of sensory block, time to onset and regression of motor block, need for supplemental anaesthesia/analgesia and time to eligibility for home discharge; safety evaluation of the study treatments. *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
STUDY END-POINTS: **Primary end-point:** 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).

STUDY SYNOPSIS, continued

STUDY END-POINTS, continued:
Secondary endpoints:
Efficacy end-points:
- Time to onset of sensory block (corresponding to readiness for surgery),
- Time to onset of motor block,
- Time to regression of sensory block
- Time to regression of motor block,
- Time to administration of rescue anaesthesia or rescue analgesia,
- Time to first post-operative analgesia,
- Time to eligibility for home discharge.

Safety end-points:
Safety and general tolerability of the study treatments on the basis of treatment-emergent adverse events (TEAEs), vital signs measurements (blood pressure, heart rate, oxygen saturation [SpO_2]) and ECG recordings.

Study participants:
180 male/female patients, 90/treatment group, aged ≥ 18 years, scheduled for distal upper limb surgery (< 60 min) under axillary brachial plexus block.

DIAGNOSIS AND CRITERIA FOR INCLUSION:
Inclusion criteria:
1. *Sex and surgery*: male and female patients scheduled for short duration (< 60 min) distal upper limb surgery under axillary nerve block anaesthesia
2. *Age*: ≥ 18 years old
3. *Body Mass Index (BMI)*: 18 - 32 kg/m^2 inclusive
4. *ASA physical status*: I-III
5. *Informed consent*: signed written informed consent before inclusion in the study
6. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study

Exclusion criteria
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 major anaesthetics
7. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may 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 will be allowed

STUDY SYNOPSIS, continued

DIAGNOSIS AND CRITERIA FOR INCLUSION, continued:

Exclusion criteria, continued:

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

STUDY PROCEDURES

The study will include a screening visit (days -14/1), a treatment phase (anaesthesia and surgical procedure: visit 2, day 1), post-operative recovery / final visit (day 1/2) and a follow up (day 7±1).

Screening (visit 1, day -14/1)

Patients scheduled for surgery of the distal upper limb will be informed about the aims, procedures and possible risks of the study and will be asked to sign the informed consent form for the inclusion in the trial. Patients will be assigned a screening number. Routine pre-surgery assessments will be performed according to the hospitals' standard procedures, and the study inclusion/exclusion criteria will be verified. A urine pregnancy test for women will be performed. The following baseline characteristics will be recorded: medical history, physical abnormalities, body weight, height, body mass index, blood pressure, heart rate, previous and concomitant medications.

Treatment Phase (visit 2, day 1)

Before the anaesthesia, patients will be questioned about adverse events occurrence and concomitant medications intake and will be assigned a consecutive randomisation number. According to the randomisation number, patients will be randomised to either Chloroprocaine HCl 2% (Test) or Ropivacaine HCl 0.75% (Reference) treatment group. Oral midazolam premedication will be administered (if necessary).

Procedure for ultrasound-guided axillary block

The arm will be externally rotated and the elbow flexed to 90 degrees. The skin surface of the axilla will be aseptically prepared. Axillary block will be performed under ultrasound guidance using standard procedures. The median, ulnar, radial and musculocutaneous nerves will be identified. A 5 cm needle will be inserted towards the 4 nerves. Once appropriate perineural needle placement is visualized, the volume (20 mL) of either Chloroprocaine HCl 2% (Test) or Ropivacaine HCl 0.75% (Reference) will be injected using a syringe. The time from needle insertion to final perineural injection (time 0 h) will be recorded.

Block assessment

Sensory and motor blocks will be evaluated in each nerve territory by an independent assessor, blinded to the anaesthetic (Test or Reference) injected. If needed, sensory and motor functions will be compared in the contralateral distal upper limb. Blocks will be assessed every 5 min until the patient is ready for surgery. Then, blocked limbs will be evaluated as soon as possible after surgery (taking into consideration the end of the surgery procedures), then every 15 min for the first hour after surgery, every 30 min for the next 2 hours and then every hour until regression of surgical anaesthesia. Time to onset of sensory and motor blocks and time to regression of sensory and motor blocks will be recorded. Sensory and motor function assessments will be performed as detailed below:

Sensory block will include thermal perception (cold spray) and sensitive perception (pin prick) assessments. The anaesthetised arm will be compared with the contralateral arm, if necessary. Assessments will be performed for each nerve territory and perceptions will be scored as being present (score 1) or absent (score 0).

STUDY SYNOPSIS, continued

Study procedures, continued

Motor block will be evaluated through specific motor tests for each nerve territory. In detail, motor tests will be: flexion of radial 3 fingers for the median nerve, extension of wrist for radial, abduction of fingers for ulnar and elbow flexion for musculocutaneous nerve. Each assessment will be scored according to the following modified Bromage scale:

Table 1 Modified Bromage scale for motor block assessment

Score	Definition
0	No movement in relevant muscle group
1	Flicker of movement in relevant muscle group
2	Ability to move relevant muscle group against gravity but inability to move against resistance
3	Reduced power but ability to move muscle group against resistance
4	Full power in relevant muscle group

Definitions

Sensory block is defined as absent thermal and sensitive perception (score 0; see above) in each nerve territory.

Onset of sensory block, corresponding to readiness for surgery, is defined as an absent cold and touch sensation in the 4 nerve territories (complete sensory block).

Motor block is defined as a motor block score of ≤ 2 on the modified Bromage scale in each nerve territory (see above; no motor block required for *successful block*). *Onset of motor block* is achieved when motor block is present in ≥ 3 nerve territories.

Time to onset of sensory block and time to onset of motor block are defined as the time period from completion of the final perineural injection (time 0 h) to achievement of complete sensory block and motor block, respectively.

Regression of sensory block will be deemed to have occurred when cold sensation and sensitive perception have returned (if assessable) in any nerve territory.

Regression of motor block will be deemed to have occurred when motor score is ≥ 3 in any nerve territory.

Successful block is defined as: 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 includes: i.v. premedication or general anaesthesia or pre- or intra-operative systemic analgesia or additional local anaesthetic infiltration.

Block failure is defined as absence of or inadequate surgical anaesthesia with the need for *supplementation* (as defined above) in the first 45 min, calculated from the time of readiness for surgery (complete sensory block).

Post-operative recovery and final visit (day 1/2)

At the end of the surgical procedure, patients will be moved to the post-operative recovery room, where they will stay until the criteria for discharge are met according to the hospitals' standard procedures. In general, to meet criteria for discharge, patients must have a score ≥ 9 on the modified Aldrete's scoring scale (Aldrete, 1998) and no feeling of pain. Vital signs, ECG (if foreseen by hospital standard procedures) and SpO_2 will be recorded. Haemodynamic variables must be stable and SpO_2 must be acceptable (> 92%) without oxygen therapy. Patients will be asked about any adverse events, with particular attention to local toxicity and neurological symptoms, such as paraesthesia of the arm, and to possible allergic reactions (e.g. urticaria). If all the criteria are met and no adverse reactions occur, the patient will be discharged according to the hospital's standard procedures.

Follow-up (Day 7±1): 6±1 days after the day of surgery, a deputy of the Investigator, not aware of the administered treatment, will contact the patients by telephone and will question them about any adverse reactions which might have occurred after discharge, with particular attention to any sign of late systemic toxicity, local toxicity, neurological symptoms and allergic reactions.

STUDY SYNOPSIS, continued

Study Procedures, continued:

Other assessments and procedures

Safety assessments

Vital signs will be recorded at the screening visit. ECG (if foreseen by standard hospital procedures), blood pressure, heart rate and SpO_2 will be monitored at baseline, during the block until the end of anaesthesia and during post-operative recovery using standard monitors, according to ASA guideline recommendations (SpO_2 should be $\geq$ 92%). Occurrence of clinically relevant hypotension or bradycardia will be monitored throughout the study and, if observed, treated according to the hospitals' standard procedures. Patients will be questioned about the occurrence of adverse events. Particular attention will be given to systemic and local toxicity symptoms, neurological symptoms and allergic reactions. In particular, patients will be instructed to report signs of systemic (central nervous system) toxicity, e.g. metallic taste, ringing in the ears etc. In addition, at every assessment time, occurrence of slurred speech will be noted.

Additional anaesthesia and Rescue analgesia

If a successful block is attained, no i.v. premedication or general anaesthesia or pre- or intra-operative systemic analgesia or additional local anaesthetic infiltration will be administered in the first 45 min calculated from the time of readiness for surgery. In the event of block failure, or after the first 45 min calculated from the time of readiness for surgery, if necessary either local anaesthesia or general anaesthesia or rescue analgesia will be administered, according to the investigator's judgment.

Premedication/sedation and Analgesia

Oral premedication with midazolam will be allowed, if necessary. No prophylactic i.v. midazolam, propofol or fentanyl will be allowed for premedication/sedation on a routine basis (if a patient needs these drugs, the block will be classified as insufficient for surgery/unsuccessful). At the end of the surgical procedure, an appropriate analgesic (e.g. mefenamic acid or paracetamol) will be administered to the patients, according to the investigator's opinion.

Blinding

Syringes for injection will be prepared by a co-investigator/pharmacist/study nurse not involved in axillary block placement or study outcome measures evaluation. An independent blinded observer will evaluate sensory and motor blocks for each patient.

Data recording

Efficacy and safety data as well as details on the surgical procedure (type, start and end time, comments) will be reported on the individual case report forms (CRF).

Sample size

Given the following definitions:
$\boldsymbol{\pi_T}$ = Proportion of success - Test (Chloroprocaine);
$\boldsymbol{\pi_R}$ = Proportion of success - Reference (Ropivacaine);
$\boldsymbol{\epsilon = \pi_T - \pi_R}$ (difference between Test and Reference proportion of success);
$\boldsymbol{\delta}$ = Non-inferiority limit;

the sample size for the one-sided hypothesis test $\mathbf{H_0: \epsilon \leq \delta}$ vs. $\mathbf{H_a: \epsilon > \delta}$ can be computed according to the following formula (Wang, 2007):

$$\mathbf{N_T = k \times N_R} \quad \text{and} \quad \mathbf{N_R = ceiling}\ \{[(Z_{1-\alpha} + Z_{1-\beta})^2 / (\epsilon - \delta)^2] \times [\pi_T (1-\pi_T)/k + \pi_R (1-\pi_R)]\};$$

where:
k = Balancing ratio between treatment arms (1 for balanced group)
$\mathbf{N_T}$ = Number of subjects included into the Per Protocol set for Test treatment group;
$\mathbf{N_R}$ = Number of subjects included into the Per Protocol set for Reference treatment group;

STUDY SYNOPSIS, continued

Randomisation

Randomisation will be stratified by centre. Patients will be allocated to the Test (Chloroprocaine) arm or Reference (Ropivacaine) arm according to a 1:1 ratio. Randomisation list will be computer generated using the PLAN procedure of the SAS® system version 9.3 (TS1M1) or higher for Windows.

Statistical analysis

Definition of analysis sets:

Safety Set: the safety set is defined as all patients who receive at least one dose of the study drug. This analysis set will be used for the safety evaluation.
Full Analysis Set (FAS): the FAS will include all randomised patients who fulfil the study protocol requirements in terms of study anaesthetics administration. This analysis set will be used for sensitivity analyses.
Per Protocol Set (PP): the PP set will include 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.

All study data will be listed by patient and will be summarised using classic descriptive statistics for quantitative variables and frequencies for qualitative variables.

Analysis will be done using SAS® version 9.3 (TS1M1) or higher for Windows.

Efficacy analysis
The efficacy analysis will be performed on the PP set (primary efficacy analysis) and FAS (sensitivity analyses). The observed response rate for each treatment group will be calculated as the proportion of subjects with a successful block (as defined above).

The proportion of subjects with a successful block will be compared between treatment groups by a binomial regression model, with the factors treatment and centre as fixed effects If the binomial regression model fails to converge, a Poisson regression model with a robust error variance (sandwich estimation) will be used instead of the binomial model. Non-inferiority of the Test in comparison with the Reference treatment will be considered proved if the lower confidence limit of the **97.5%** one-sided confidence interval of the difference between treatments is greater than the non-inferiority margin **$\delta = -0.1$**.

Secondary variables (time to onset of sensory block [readiness for surgery], time to onset of motor block, time to sensory and motor block regression, time to eligibility for home discharge, time to rescue anaesthesia or analgesia, time to post-surgery analgesia) will be presented using Kaplan-Meier curves and will be compared between treatment groups by log rank test. All tests on the secondary variables will be performed with a nominal two-sided type I error $\alpha = 0.05$.

STUDY SCHEDULE

ACTIVITIES	Visit 1 - Screening	Visit 2 - Treatment	Post-operative recovery, final visit	Telephonic Follow-up
Visit	**Days -14/1**	**Day 1**	**Day 1/2**	**Day 7±1**
Informed consent	x			
Demography	x			
Medical/surgical history	x			
Physical abnormalities	x			
Previous and concomitant medications	x	x	x	x
Height	x			
Body weight	x			
Vital signs (blood pressure, heart rate)[1]	x	x	x	
SpO_2[2]		x	x	
ECG[1]		x	x	
Pregnancy test (urine)	x			
Eligibility evaluation	x	x		
Enrolment and randomisation[3]		x		
Oral midazolam premedication (if necessary)[4]		x		
Anaesthesia (IMP administration)[5]		x		
Sensory block assessment[6]		x		
Motor block assessment[6]		x		
Surgery (< 60 min)		x		
Aldrete's scoring scale[7]			x	
Home discharge[7]			x	
Meals[9]			x	
Adverse events monitoring[8]	x	x	x	x

1. *Vital signs at screening; vital signs and ECG (if foreseen by the standard hospital procedures) at baseline, during the block until the end of the anaesthesia and during post-operative recovery (final visit)*
2. *SpO_2 before the block (baseline), during the block until the end of the anaesthesia and during post-operative recovery (final visit)*
3. *On day 1, before any study procedures subjects will be randomised to either Chloroprocaine HCl 2% or Ropivacaine HCl 0.75% treatment group*
4. *Oral premedication with midazolam is allowed, if necessary*
5. *Patients will receive anaesthetic block with either Chloroprocaine or Ropivacaine, before surgery, according to the randomisation list and parallel-group design*
6. *Sensory and motor blocks will be assessed by a blinded assessor after block placement, every 5 min until the patient is ready for surgery, as soon as possible after surgery, then every 15 min for the first hour after surgery, every 30 min for the next 2 h and then every 1 h until regression of the blocks.*
7. *Patients will be discharged on Day 1 or on a following day after the criteria for discharge are met and according to the hospital's standard procedures. In case of discontinuation, subjects will undergo an early termination visit (ETV)*
8. *AEs monitored from the screening visit, immediately after informed consent signature, up to the telephonic follow-up*
9. *Meals will be served according to the hospital's standard procedures*

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FIGURES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOA	Attributable-Legible-Contemporaneous-Original-Accurate
ANOVA	Analysis of Variance
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BP	Blood Pressure
BW	Body Weight
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CRS	Clinical Study Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
ETV	Early Termination Visit
FAS	Full Analysis Set
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IMP	Investigational Medicinal Product
IUD	Intra-Uterine Device
IV	Intravenous
IVRA	Intravenous Regional Anaesthesia
LSLV	Last Subject Last Visit
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MF	Missing as Failure
MI	Multiple Imputation
NA	Not Applicable
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
PP	Per Protocol
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SmPC	Sumary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Perypheral oxygen saturation
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
WC	Worst Case
WHODDE	World Health Organisation Drug Dictionary Enhanced

1 INTRODUCTION

1.1 Background

1.1.1 Local anaesthesia

Local anaesthesia is employed successfully in a wide variety of surgical procedures to produce the regional blockade of sensory and motor fibres without impacting the consciousness of patients. Compared to general anaesthesia, local anaesthetics present many significant advantages, especially in terms of reduced recovery time and enhanced safety.

While practice of outpatient surgery is steadily growing, the ideal local anaesthetic should provide a rapid onset plus adequate potency and duration of action, combined with a favourable safety profile and very low risk of systemic toxicity. Furthermore, the patient should be able to recover motor and sensory functions shortly after surgery, and be discharged on the same day with manageable post-surgery pain and discomforts (1-3).

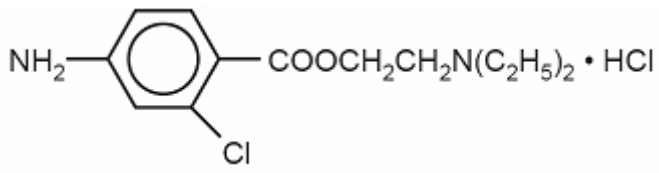
Anesthesiologists may choose among diverse local anaesthetics for infiltration, peripheral nerve blockade and epidural anaesthesia. Among these, lidocaine has been the most widely used for decades, though several other agents present the same efficacy and a safer profile.

In general, the selection of the local anaesthetic primarily depends on the duration of the procedure planned. Bupivacaine, for instance, is the privileged choice for lengthy procedures, i.e. procedures of more than 90 minutes of duration, while it also presents a longer latency period, besides being one of the most painful agents during injection (3). Other agents exist with moderate potency and duration, such as ropivavaine, mepivacaine and prilocaine, that are diffusely used (1,4). Chloroprocaine and articaine are among the anaesthetic agents characterized by shortest latency and duration of action, though articaine presents a higher reported risk of neural toxicity (1,3).

1.1.2 Chloroprocaine

Chloroprocaine hydrochloride (Chloroprocaine HCl [benzoic acid, 4-amino-2-chloro-2-(diethylamino) ethyl ester, monohydrochloride]; Figure 1.1.2.1) is a short-acting local anaesthetic belonging to the amino-ester class, characterized by a rapid onset of action (1,4) (usually 6 to 12 minutes) and anaesthesia duration up to 60 min, depending on the amount used and the route of administration. *In-vitro* chloroprocaine half-life is approximately 21-25 seconds.

Figure 1.1.2.1 Chemical structure of chloroprocaine hydrochloride



There is a long history of use of chloroprocaine and the amino ester class of anaesthetics in USA, Canada and Switzerland. Firstly introduced in 1952 (8), chloroprocaine has been

employed as local anaesthetic for decades now, though past episodes of neurological toxicity in patients exposed to spinal anaesthesia with bisulfite-containing chloroprocaine had discouraged a larger use (9-11). It was later demonstrated that neurological complications were associated with the preservative agents added to chloroprocaine formulations (12). As a consequence, preservative-free and also EDTA-free formulations have been developed, and are now available, which prevent these severe adverse episodes and guarantee a safer profile compared to other local anaesthetics (11).

Similar to lidocaine, chloroprocaine is used for short-duration surgical procedures (45-60 minutes), mainly in the ambulatory setting, when a fast recovery and prompt home readiness are required (2,4). In the literature, following the chloroprocaine-operated peripheral nerve block, reported median time to eligibility for home discharge ranged from about 2 to 5 hours (13-16).

Indeed, the pharmacological properties of chloroprocaine render it unique. Chloroprocaine presents the shortest onset of action and is rapidly metabolized in the circulation by plasma esterase hydrolytic activity. This shortens the duration of action (depending on the amount used and the administration route) and, importantly, prevents the drug's plasma accumulation (1,4) and related risks of toxic systemic spread (4,6,18,19).

Chloroprocaine dose level for each anaesthesia technique are included in the SmPCs of the listed reference drugs (Nesacaine® 1,2 and 3%, AstraZeneca; Chloroprocaine HCl 1 and 2%, Bedford Laboratories; Ivracain® 1% Sintetica SA). In particular, chloroprocaine 2% solutions have been marketed in USA and Canada for several years and are indicated for the production of local anaesthesia by peripheral nerve block as well as via other administration routes.

1.1.3 Safety of local anaesthetics

If appropriately administered, in terms of dosage and anatomical location, local anaesthetics are relatively free of adverse effects. In general, toxicity following local anaesthesia is more often engendered by the accidental intravascular or subarachnoid injection of the drug or the administration of an excessive dose. Fortunately severe complications are rare and their incidence has been significantly reduced in the last decades (5). To simplify, three main categories of potential toxicity from loco-regional anaesthesia techniques may be considered: systemic toxicities, peripheral nerve injuries and other local tissue toxicities, such as allergic reactions (3,5-7).

Systemic toxicity ranges from mild systemic symptoms, such as visual and auditory disturbances, drowsiness, circumoral numbness, and agitation, to serious signs of central nervous system (CNS) depression, such as seizures, respiratory depression and respiratory arrest. Furthermore, the systemic spread of local anaesthetics may exert a direct action on cardiovascular functions, leading to hypertension, hypotension, tachycardia, bradycardia, ventricular arrhythmias and cardiac arrest (3,5,6).

Peripheral nerve injuries following peripheral nerve blocks are also rare, though distinctions can be made between major complications, which result in permanent nerve damage and occur with a 1.5:10000 incidence, and more frequent transient neurological deficits (7). For instance, an incidence of 8-10% is reported for episodes of transient paraesthesia. However,

regardless of the anaesthetic administered, the use of ultrasound guidance for peripheral nerve blocks has now improved the efficacy and safety of the anaesthetic techniques (7; § 1.1.4). Furthermore, the onset of toxicity generally occurs during, or shortly after, the surgical operation, thus can be immediately caught and appropriately managed.

Chloroprocaine favourable safety profile for spinal anaesthesia is largely recognized in the literature (18-21). Currently available literature sources, mostly clinical trials, occasionally report episodes of mild systemic toxicity following chloroprocaine loco-regional anaesthesia, while other studies found no toxicities at all (0-1% for peripheral nerve blocks (14,15,22-24); up to 8-37.3% for intravenous regional anaesthesia – IVRA (25); up to 12.5-55% for epidural [13,17]).

1.1.4 Ultrasound-guided axillary block

Axillary block for brachial plexus anaesthesia is a very popular anaesthetic technique for hand and forearm surgery, especially due to the very low incidence of complications compared to other brachial plexus block techniques (26). For this technique to be successful, deposition of local anaesthetic adjacent to four nerves (the median, radial, ulnar and musculocutaneous nerves) is required.

Historically, single-injection techniques have not provided reliable blockade in the musculocutaneous and radial verve territories, but success rates have greatly improved with multiple-injection techniques using nerve stimulation and more recently using ultrasound guidance. The latter has become very common in clinical practice thanks to the refinement of ultrasound technology and ultrasound-guided block techniques, and is gradually replacing nerve stimulator-guided approach (26).

Ultrasound visualization of target nerves, needle and injectate spread has in fact been associated with improved block success rates, decreased block onset times and a decrease in the local anaesthetic dose needed (27; 28-35). With ultrasound-guideded axillary block, damage to important structures like nerves and vessels, during the injections, can be avoided and the risk of accidental nerve damage can be reduced, although care should be continually exercised using standard safety precautions to minimize any possible risk associated with the technique (26).

1.2 Rationale

Ambulatory surgical procedures are steadily increasing in Europe and USA. The use of short-acting local anaesthetic agents such as chloroprocaine permits a rapid onset of anaesthesia for short duration surgery and early recovery profiles, offering the advantage of early home discharge.

There is a long history of use of chloroprocaine and the amino ester class of anaesthetics in USA, Canada and Switzerland. In particular, chloroprocaine solutions (i.e. Nesacaine® 1, 2, 3%, Astra-Zeneca; Chloroprocaine HCl 2, 3%, Bedford Laboratories) have been marketed in USA and Canada for several years and are indicated for the production of local anaesthesia by peripheral nerve block as well as via other administration routes (see corresponding SmPCs).

Sintetica SA, Switzerland, received marketing approval for 0.5% Chloroprocaine HCl Injection for IVRA (Ivracain®) in Switzerland in 1996. In 2012, preservative-free Chloroprocaine HCl 1% injection, Sintetica SA (Switzerland) has been approved for spinal-intrathecal anaesthesia, under the brand name of Ampres/Clorotekal, in several European countries (i.e. Germany, UK, Austria, Belgium, France, Ireland, Italy, Poland and Spain).

Whereas Chloroprocaine HCl 2% solutions are presently on the market in USA and Canada for the production of local anaesthesia by peripheral nerve block and other administration routes, in Europe this local anaesthetic is not presently marketed as a 2% solution for the above reported indications.

As part of a development programme for the preservative-free Chloroprocaine HCl Injection products (i.e. Chloroprocaine 0.5, 2 and 3%, Sintetica SA, Switzerland) in EU member states, the present study has been designed to evaluate the non-inferiority of Chloroprocaine HCl 2% (Sintetica SA; Test) with respect to Ropivacaine HCl 0.75% (Naropin®, AstraZeneca GmbH, Germany; Reference) in axillary brachial plexus blockade in men and women undergoing short duration distal upper limb surgery including hand, wrist and forearm procedures. Ropivacaine HCl 0.75% has been chosen as the active control because commonly used in Germany, Switzerland and other European countries in brachial plexus block procedures (see Ropivacaine 7.5 mg/mL SmPC).

The doses of the two local anaesthetics for this study (20 mL) have been chosen according to the products' SmPCs and the use of ultrasound-guided as compared to the nerve stimulation technique for the axillary plexus block.

1.3 Risk and benefits

There are no direct benefits to the patients participating in the study.

The risks for the study patients are anticipated to be low, considering that the ultrasound-guided axillary approach for brachial plexus blockade is a well-known technique routinely used in the clinical setting and that the two local anaesthetics investigated in the study have been on the market under different brand names in USA and Canada for several years for the proposed indications, and the potential side effects, contraindications and special warnings are well described in the corresponding product information (see Nesacaine® and Naropin® SmPCs).

Axillary block for brachial plexus anaesthesia has been reported to be the safest of the brachial plexus blockade techniques because of the reduced risk to surrounding structures such as the risk of phrenic nerve blockade and/or pneumothorax. The rates of complications with axillary block are quite low and consist mainly in haematomas and pain at the injection site. The general risks of accidental intravascular and intraneural injection, however, still exist, but are markedly reduced with the use of ultrasound visualization of the 4 concerned nerves. In any case, care will be continually exercised using standard safety precautions to minimize the risks associated with the technique.

Allergic reactions with local anaesthetics are rare but could occur in patients hypersensitive to ester groups and could consist of pruritus, urticaria, edema and tachycardia.

Central nervous system and cardiovascular system adverse reactions are generally dose-related and occur only with high plasma concentrations of local anaesthetics. These reactions are not expected in the present study. However, careful and constant monitoring of cardiovascular and respiratory vital signs and patients status will be performed throughout the study procedures.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to evaluate the non-inferiority of Chloroprocaine HCl 2%, Sintetica SA (Test) versus Ropivacaine HCl 0.75% (Naropin®, AstraZeneca; Reference) 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.

2.2 Secondary objectives

The secondary study objectives are:

- To compare Test and Reference products in terms of the time to onset of sensory block (readiness for surgery), time to regression of sensory block, time to onset and regression of motor block, need for supplemental anaesthesia/analgesia and time to eligibility for home discharge
- To evaluate the safety and tolerability profile of the study treatments.

3 CLINICAL SUPPLIES

3.1 Treatment

3.1.1 Description of products

The analytical certificates will be enclosed with the investigational medicinal products (IMPs).

3.1.1.1 Test product

TEST (T)

IMP	Chloroprocaine HCl 2% (20 mg/mL)
Distributor	Sintetica S.A., Switzerland
Manufacturer	Sintetica S.A., Switzerland
Pharmaceutical form	Solution for injection (ampoule)
Dose	20 mL (400 mg), approximately 5 mL (100 mg) per nerve
Administration route	Axillary injection (axillary brachial plexus block)

3.1.1.2 Reference product

REFERENCE (R)

IMP	Naropin®, 0.75% (7.5 mg/mL)
Active substance	Ropivacaine HCl
Distributor	AstraZeneca GmbH, Germany
Pharmaceutical form	Solution for injection (ampoule)
Dose	20 mL (150 mg), approximately 5 mL (37.5 mg) per nerve
Administration route	Axillary injection (axillary brachial plexus block)

3.1.2 Dose regimen

Patients will be randomised to one of the two treatment groups to receive either Chloroprocaine HCl 2% (Test) or Ropivacaine HCl 0.75% (Reference) as anaesthetic before surgery, according to the randomised, parallel-group design of the study.

Patients in the Test product group will receive a single total dose of 20 mL Chloroprocaine HCl 2% (corresponding to 400 mg) and patients in the Reference group will receive a single total dose of 20 mL Ropivacaine HCl 0.75% (corresponding to 150 mg).

3.1.3 Route and method of administration

Both anaesthetics will be administered by the axillary nerve route, as described below.

Test and reference individual ampoules (one ampoule of anaesthetic per patient) will be opened just before the administration. Syringes for injection will be prepared by a co-investigator/pharmacist/study nurse not involved in axillary block placement or study

outcome measures evaluation. Details on the anaesthetic preparation in syringes for injection will be given in the study manual.

For the placement of the axillary block, the following procedure will be used in both anaesthetic treatment groups:
The arm will be externally rotated and the elbow flexed to 90 degrees. The skin surface of the axilla will be aseptically prepared. Axillary block will be performed under ultrasound guidance using standard procedures. The median, ulnar, radial and musculocutaneous nerves will be identified. A 5 cm needle will be inserted towards the 4 nerves. Once appropriate perineural needle placement is visualized, the volume (20 mL) of either Chloroprocaine HCl 2% (Test) or Ropivacaine HCl 0.75% (Reference) will be injected using a syringe. The time from needle insertion to final perineural injection (time 0 h) will be recorded.

3.1.4 Investigational product distribution

The test and reference products will be administered by the investigator or by his/her deputy. The investigational products will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

3.2 Packaging and labelling

Packaging and labelling will be carried out by the Sponsor according to the randomisation list. Labelling in local language will be applied in such a way that it should not obscure the original label and will report all the information requested according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in The rules governing medicinal products in the European Community, Volume 4).

Labelling on packages will report:

a) Name, address and telephone number of the sponsor and CRO;
b) Pharmaceutical dosage form, route of administration, quantity of dosage units, the name/identifier and strength/potency;
c) Batch number;
d) Study Nr.;
e) The study subject identification number/treatment number;
f) Expiry in month/year format and in a manner that avoids any ambiguity;
g) Investigator's name;
h) Directions for use;
i) “For clinical trial use only” wording;
j) The storage conditions;

Further details on the products packaging will be given in the study manual.

3.3 Storage conditions

The test product will be stored at 15 - 25°C in a dry locked place, sheltered from light. The reference product will be stored at < 30°C and must not be frozen.

3.4 Drug accountability

The test and reference investigational products will be provided directly to the investigator by the sponsor, in excess of the amount necessary for the study (at least 25% excess).

After receipt of the investigational products supply, the pharmacist will confirm in writing by signing and dating standard drug accountability forms.

At the end of the study, used, unused and partially used supplies of test and reference investigational products provided by the sponsor/manufacturer will either be destroyed on site (upon written authorisation) or returned to the sponsor/manufacturer, after assessment of drug accountability.

4 INVESTIGATIONAL PLAN

4.1 Overall study design

This will be a prospective, randomised, multi-centre, active-controlled, blind-observer, parallel-group, non-inferiority study.

4.2 Discussion of design

The study has been designed to evaluate the non-inferiority of Chloroprocaine HCl 2% (Test) with respect to Ropivacaine HCl 0.75% (Reference) in axillary brachial plexus blockade in men and women undergoing short duration distal upper limb surgery. In designing the study the following guidelines were taken into consideration: ICH E9 guideline on Statistical principles for clinical trials (36); the Guideline on the choice of the non-inferiority margin (CPMP/EWP/2158/99; 37); and the Points to consider on switching between superiority and non-inferiority guideline (CPMP/EWP/482/99; 38). A non-inferiority margin of 10% (**δ = -0.1**) was set in accordance to the information in published works (27,30,39-42) on the success rates with local amide anaesthetics using ultrasound-guided axillary block. No placebo could be investigated in this trial in a third treatment arm because the study treatment consists of local anaesthesia before a surgical procedure and an active agent must be used in all cases.

Distal upper limb surgeries, which include hand, wrist and forearm surgeries, have been selected because routinely performed under axillary plexus block.

Ropivacaine HCl 0.75% has been chosen as the active control because commonly used in Germany, Switzerland and other European countries in brachial plexus block procedures (see Naropin® [Ropivacaine HCl] 0.75% SmPC).

Ultrasound-guided axillary block for brachial plexus anaesthesia is a popular anaesthetic technique for distal upper limb surgery and is considered the safest approach because of reduced risk to surrounding structures (26).

Each patient will be allocated to a treatment arm according to a computer-generated randomisation list.

The study will be observer-blind. Syringes for injection will be prepared by a co-investigator/pharmacist/study nurse not involved in axillary block placement or study outcome measures evaluation. An independent blinded observer will evaluate sensory and motor blocks for each patient.

5 STUDY POPULATION

5.1 Target population

One hundred and eighty (180) male/female patients, 90/treatment group, aged ≥ 18 years, scheduled for distal upper limb surgery (< 60 min) under axillary brachial plexus block.

5.2 Inclusion criteria

To be enrolled in this study, subjects must fulfil all these criteria:

1. *Sex and surgery*: male and female patients scheduled for short duration (< 60 min) distal upper limb surgery under axillary nerve block anaesthesia
2. *Age*: ≥ 18 years old
3. *Body Mass Index (BMI)*: 18 - 32 kg/m^2 inclusive
4. *ASA physical status*: I-III
5. *Informed consent*: signed written informed consent before inclusion in the study
6. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study

5.3 Exclusion criteria

Subjects meeting any of these criteria will not be enrolled in the study:

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 major anaesthetics
7. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may 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 will be 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

5.3.1 Not allowed treatments

No medication known to interfere with the extent of regional blocks (see chloroprocaine and ropivacaine SmPCs) will be allowed for 2 weeks before the start of the study and during the whole study duration. Hormonal contraceptives for females are allowed.

5.3.2 Additional anaesthesia and rescue analgesia

If a successful block is attained, no i.v. premedication or general anaesthesia or pre- or intra-operative systemic analgesia or additional local anaesthetic infiltration will be administered in the first 45 min calculated from the time of readiness for surgery. In the event of block failure, or after the first 45 min calculated from the time of readiness for surgery, if necessary local anaesthesia, general anaesthesia or rescue analgesia will be administered, according to the investigator's judgment.

5.3.3 Premedication/sedation and analgesia

Oral premedication with midazolam will be allowed, if necessary. No prophylactic i.v. midazolam, propofol or fentanyl will be allowed for premedication/sedation on a routine basis (if a patient needs these drugs, the block will be classified as insufficient for surgery). At the end of the surgical procedure, an appropriate analgesic (e.g. mefenamic acid or paracetamol) will be administered to the patients, according to the investigator's opinion.

6 STUDY SCHEDULE

The schedule of the study is summarised at page 14.

6.1 Study visits and procedures

The study protocol foresees a screening visit, 1 study treatment for each patient, followed by post-operative recovery, final visit and follow up. Maximum study duration will be approx. 22 days, screening visit and follow-up included. A written informed consent will be obtained before any study assessment or procedure.

The first subject first visit (FSFV) is defined as the 1st visit performed at the clinical centre by the 1st screened subject. The last subject last visit (LSLV) is defined as the telephonic follow-up performed by the last subject, i.e. the last visit foreseen by the study protocol, independently of the fact that the subject is a completer or a withdrawn subject.

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening – visit 1: between day -14 and day 1
- **Interventional phase**
  - Visit 2 – day 1: Anaesthesia and surgery
- **Follow-up phase**
  - Post-operative recovery – day 1 (immediately after surgery)
  - Final visit/early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV)
  - Telephonic follow-up – day 7±1 (6±1 days after surgery)

	Day	Procedures/Assessments	Notes
Screening – Visit 1	*From day -14 to day 1*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S001, S002, etc.) ➢ Demographic data ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (BW, height, body mass index, vital signs, physical abnormalities) ➢ Urine pregnancy test for women ➢ Eligibility evaluation ➢ AE monitoring	
Treatment - Visit 2	*Day 1*	➢ Eligibility evaluation ➢ Enrolment and randomisation ➢ Oral midazolam premedication (if necessary) ➢ Anaesthesia administration ➢ Sensory and motor block assessments ➢ Vital signs, SpO_2 and ECG (if foreseen by standard hospital procedures) ➢ Surgery (< 60 min) ➢ AEs and concomitant medications	
Post-operative recovery and Final Visit/ETV	*Day 1/2 or upon discontinuation in case of ETV*	➢ Patients moved to post-recovery room (after surgery) ➢ Aldrete's scoring scale ➢ Vital signs, ECG (if foreseen by standard hospital procedures) and SpO_2 ➢ AE and concomitant medications ➢ Discharge (when criteria for discharge are met and according to the hospital's standard procedures)	Meals (lunch [and dinner only if applicable]) will be served after surgery and recovery according to the hospital's standard procedures. Patients will be discharged on Day 1 or on a following day after the criteria for discharge are met and according to the hospital's standard procedures. Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions
Telephonic Follow-up	*Day 7±1*	➢ AE and concomitant medications	

6.2 Diet and lifestyle

Study participants will undergo study procedures as outpatients or inpatients, according to the decision of the study investigator. Patients will arrive at the clinical centre either in the morning of the scheduled surgery day or the previous evening, according to the hospital requirements, and will be discharged according to the hospital procedures after meeting the criteria for discharge (on Day 1 or on a following day).

On day 1, patients will be under fasting conditions before surgery. Clear fluids intake is allowed until 2 h before surgery.

The patients will remain under fasting conditions until surgery has been completed and according to the investigator's opinion. Meals will be served according to the hospital's standard procedures.

7 DESCRIPTION OF SPECIFIC PROCEDURES

7.1 Physical examination

Full physical examinations will be performed at the screening visit (ETV). Information about the physical examination will be recorded by the investigator. Any abnormalities will be recorded.

Information about the type of distal upper limb surgery will be recorded.

7.1.1 Body weight

Body weight (BW) will be recorded at the screening visit.

Patients will be weighed (kg) lightly clothed without shoes. Height will be measured at screening only and BMI will be recorded. BMI will be calculated as weight [kg]/(height [m] x height [m]).

7.1.2 Vital signs

Patients' blood pressure (BP) and heart rate (HR) will be measured by the investigator or his/her deputy after 5 min at rest (sitting position) at the screening visit. Blood pressure, HR and SpO_2 will be monitored using standard monitors, according to ASA recommendations, at baseline (before block placement), during the block until the end of the anaesthesia.

The following normal ranges for haemodynamic variables will be used:

- Systolic Blood Pressure: 100-139 mmHg
- Diastolic Blood Pressure: 50-89 mmHg
- Heart Rate: 50-90 beats/min
- Peripheral Oxygen Saturation: ≥ 95%

Blood pressure, heart rate and SpO_2 will be monitored also at post-operative recovery and final visit. SpO_2 should be ≥ 92% during the monitoring period.
To meet criteria for discharge, the patients' haemodynamic variables must be stable and SpO_2 must be acceptable (> 92%).

Occurrence of clinical relevant hypotension and bradycardia will be monitored throughout the study and, if observed, treated according to the hospitals' standard procedures.

7.1.3 ECGs

ECG will be monitored using standard monitors at baseline (before block placement), during the block and at post-operative recovery / final visit (if foreseen by standard hospital procedures).

The following normal ranges for ECG parameters will be used:

- Heart Rate: 50-90 beats/min
- PR Interval: 100-220 msec
- QRS Duration: ≤ 120 msec
- QT Interval: ≤ 500 msec

7.1.4 Pregnancy test

A urine pregnancy test for women will be performed at screening (Visit 1).

7.1.5 Block assessment

Sensory and motor blocks will be evaluated in each nerve territory by an independent assessor, blinded to the anaesthetic (Test or Reference) injected. If needed, sensory and motor functions will be compared in the contralateral distal upper limb. Blocks will be assessed every 5 min until the patient is ready for surgery. Then, blocked limbs will be evaluated as soon as possible after surgery (taking into consideration the end of surgery procedures), every 15 min for the first hour after surgery, every 30 min for the next 2 hours and then every hour until regression of surgical anaesthesia. Time to onset of sensory and motor blocks and time to regression of sensory and motor blocks will be recorded.
Block assessment times should not deviate more than the recommended deviation time ranges summarised in the following table.

Table 7.1.5.1 Recommended maximal deviations from the scheduled block assessment times

Blocks assessment times	Deviation
Every 5 min until readiness for surgery	± 1 min
Immediately after surgery	---
15 min after surgery	± 1 min
30 min after surgery	± 2 min
45 min after surgery	± 2 min
1 h after surgery	± 3 min
1.5 h after surgery	± 3 min
2 h after surgery	± 5 min
2.5 h after surgery	± 5 min
3 h after surgery and then every hour until regression of anaesthesia	± 5 min

Any deviation from the scheduled block assessment times outside the recommended ranges will be verified through Data Clarification Forms. If for a subject more than 20% of the actual block assessment times will be outside the recommended ranges, the concerned subject will be excluded from the Per Protocol set.

Sensory and motor function assessments will be performed as detailed below:

Sensory block will include thermal perception (cold spray) and sensitive perception (pin prick) assessments. The anaesthetised arm will be compared with the contralateral arm, if necessary. Assessments will be performed for each nerve territory and will be scored as being present (score 1) or absent (score 0).
Sensory block is defined as a sensory block score of 0.

Onset of sensory block, corresponding to readiness for surgery, is defined as an absent cold and touch sensation in the 4 nerve territories (complete sensory block).

Motor block will be evaluated through specific motor tests for each nerve territory. In detail, motor tests will be: flexion of radial 3 fingers for the median nerve, extension of wrist for radial, abduction of fingers for ulnar and elbow flexion for musculocutaneous nerve. Each assessment will be scored according to the following modified Bromage scale (39):

Table 7.1.5.2 Modified Bromage scale for motor block assessment

Score	Definition
0	No movement in relevant muscle group
1	Flicker of movement in relevant muscle group
2	Ability to move relevant muscle group against gravity but inability to move against resistance
3	Reduced power but ability to move muscle group against resistance
4	Full power in relevant muscle group

Motor block is defined as a motor block score of ≤ 2 on the modified Bromage scale.

Onset of motor block is achieved when motor block is present in ≥ 3 nerve territories. No motor block is required for ***successful block***.

Regression of sensory block will be deemed to have occurred when cold sensation and sensitive perception have returned (if assessable) in any nerve territory.

Regression of motor block will be deemed to have occurred when motor score is ≥ 3 in any nerve territory.

7.2 Procedures for post-operative recovery and final visit

At the end of the surgical procedure, patients will be moved to the post-operative recovery room, where they will stay until the criteria for discharge are met according to the hospitals' standard procedures. In general, to meet criteria for discharge, patients must have a score ≥ 9 on the modified Aldrete's scoring scale (43) and no pain. Haemodynamic variables must be stable and SpO_2 must be acceptable (> 92%) without oxygen therapy. Patients will be asked about any adverse events, with particular attention to local toxicity and neurological symptoms, such as paraesthesia of the arm, and to possible allergic reactions (e.g. urticaria). If all the criteria are met and no adverse reactions occur, the patient will be discharged according to the hospital's standard procedures.

7.3 Procedures for telephonic follow-up

On day 7±1 (6±1 days after the day of surgery), a deputy of the Investigator, not aware of the administered treatment, will contact the patients by telephone and will question them about any adverse reactions which might have occurred after discharge, with particular attention to any sign of late systemic toxicity, local toxicity, neurological symptoms and allergic reactions.

7.4 Assessment of symptoms of systemic and local toxicity

Particular attention will be given to systemic and local toxicity symptoms, neurological symptoms and allergic reactions. In particular, patients will be instructed to report signs of systemic (central nervous system) toxicity, e.g. metallic taste, ringing in the ears etc. In addition, at every assessment time, occurrence of slurred speech will be noted.

7.5 Data recording

Efficacy and safety data will be reported on the individual case report forms (CRF).

Details on the surgical procedure, i.e. type of surgery, start time, end time and comments will also be reported on the individual CRF.

8 ASSIGNMENT OF STUDY TREATMENT

8.1 Randomisation

The randomisation list will be computer generated by the Biometry Unit of the Clinical Contract Research Organization (CRO), using the PLAN procedure of the SAS® system version 9.3 (TS1M1) (44) or higher for Windows (the version will be stated in the final clinical study report). The randomisation list will be attached to the final clinical study report. Randomisation will be stratified by centre.

8.2 Treatment allocation

Patients will be allocated to the Test (Chloroprocaine) arm or Reference (Ropivacaine) arm in a 1:1 ratio according to the study randomisation list.

Each study centre will receive a set of Test and Reference treatments. Each treatment ampoule will be individually labelled and packaged (see § 3.2).

Randomisation number will be given to the patients on study Day 1 and will be used to allocate each patient to a treatment group, as detailed above.

8.3 Blinding

This is an observer-blind study. No masking procedure will be applied.

Syringes for injection will be prepared by a co-investigator/pharmacist/study nurse not involved in axillary block placement or study outcome measures evaluation. An independent blinded observer will evaluate sensory and motor blocks for each patient.

Emergency envelopes containing individual randomisation codes will be sent to the clinical centres. Breaking of an individual randomisation code during the study is allowed only when knowledge of the code is essential for the patient's health. In this case, only the envelope related to the concerned subject will be opened. Individual code breaking will be clearly reported in the patient CRF and on the envelope.

The clinical centres will also receive individual kit replacement envelopes. If a reserve kit needs to be used, the kit replacement envelope will be opened and the injectable solution will be prepared in such a way that the observer blind condition of the study is maintained. The date and the reason for kit replacement envelope opening will be recorded on the envelope.
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9 EVALUATION PARAMETERS

9.1 Study variables

9.1.1 Primary end-point

The primary study end-point will be the proportion of subjects (%) with a successful block for distal upper limb surgeries, without any supplementation (i.e. no i.v. premedication or general anaesthesia or pre- or intra-operative systemic analgesia or additional local anaesthetic infiltration) in the first 45 min, calculated from the time of readiness for surgery.

9.1.2 Secondary end-points

Efficacy end-points:

- Time to onset of sensory block (corresponding to readiness for surgery),
- Time to onset of motor block,
- Time to regression of sensory block,
- Time to regression of motor block,
- Time to administration of rescue anaesthesia or rescue analgesia,
- Time to first post-operative analgesia,
- Time to eligibility for home discharge.

Safety end-points:

- Treatment-emergent adverse events (TEAEs),
- Vital signs measurements (blood pressure, heart rate, SpO_2)
- ECG recordings (if foreseen by hospital standard procedures)

9.2 Efficacy assessments

Sensory and motor block assessment procedures and evaluations are detailed in § 7.1.4.

Efficacy assessments are based on the following variables:

Parameter	Description
Proportion of subjects with successful block	Number of subjects with a successful block (as defined below*) divided by the number of subjects in the efficacy analysis set (FAS and PP set, see § 10.1.1)
Time to onset of sensory block (corresponding to time to readiness for surgery) (min)	Time period from completion of the final perineural injection (time 0 h) to achievement of sensory block in the 4 nerve territories (as defined in § 7.1.4)
Time to onset of motor block (min)	Time period from completion of the final perineural injection (time 0 h) to achievement of motor block (as defined in § 7.1.4).
Time to regression of sensory block (min)	Will be deemed to have occurred when cold sensation and sensitive perception have returned (if assessable) in any nerve territory.
Time to regression of motor block (min)	Will be deemed to have occurred when motor score is ≥ 3 in any nerve territory.
Time (h) to administration of rescue anaesthesia or rescue analgesia	Time from completion of the final perineural injection (time 0 h) to administration of first rescue anaesthesia or analgesia (supplementation) (if applicable)
Time (h) to first post-operative analgesia	Time from completion of the final perineural injection (time 0 h) to first post-operative analgesia
Time (h) to eligibility for home discharge	Time from completion of the final perineural injection (time 0 h) to the time when the criteria for discharge are met, even if, according to the hospital procedures, the patient is discharged from the hospital at a later time

****Successful block*** is defined as: 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 includes: i.v. premedication or general anaesthesia or pre- or intra-operative systemic analgesia or additional local anaesthetic infiltration.

Block failure is defined as: absence of or inadequate surgical anaesthesia with the need for *supplementation* (as defined above) in the first 45 min, calculated from the time of readiness for surgery (complete sensory block).

9.3 Safety assessments

Safety and general tolerability of the investigational anaesthetic will be based on TEAEs, vital signs measurements (blood pressure, heart rate, SpO_2) and ECG recordings (if applicable).

In particular, ECG, blood pressure, heart rate and SpO_2 will be monitored before the block for baseline assessment, during the block until the end of anaesthesia (ECG if foreseen by standard hospital procedures), using standard monitors, according to ASA guideline recommendations (SpO_2 should be $\geq$ 92%). These variables will be monitored also during post-operative recovery. To meet criteria for home discharge, haemodynamic variables must be stable and SpO_2 must be acceptable (> 92%) without oxygen therapy.

Occurrence of clinically relevant hypotension or bradycardia will be monitored throughout the study and, if observed, treated according to the hospitals' standard procedures.

Patients will be questioned about the occurrence of treatment-emergent adverse events (TEAEs). Particular attention will be given to systemic and local toxicity symptoms, neurological symptoms and allergic reactions. In particular, patients will be instructed to report signs of systemic (central nervous system) toxicity, e.g. metallic taste, ringing in the ears etc. In addition, at every assessment time, occurrence of slurred speech will be noted.

10 STATISTICAL METHODS

The data documented in this study and the parameters measured will be evaluated and compared using classic descriptive statistics, i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables.

Not available data will be evaluated as "missing values". The statistical analysis will be performed using SAS® system version 9.3 (TS1M1) (44) or higher for Windows (the version will be stated in the final clinical study report).

10.1 Analysis Sets

10.1.1 Definitions

A subject will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures.

A subject will be defined as eligible if he/she meets all the inclusion/exclusion criteria. Otherwise he/she will be defined as a screen failure.

A subject will be defined as enrolled in the study if he/she is included into the interventional phase of the study. The enrolment will be performed through randomised allocation to a treatment arm.

A subject will be defined as randomised in the study when he/she is assigned to a randomised treatment arm.

- Enrolled set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics
- Full Analysis Set (FAS): all randomised patients who fulfil the study protocol requirements in terms of study anaesthetics administration. This analysis set will be used for sensitivity analyses
- Per Protocol set (PP): 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
- Safety set: all patients who receive at least one dose of the investigational medicinal product(s). This analysis set will be used for the safety analyses

Each subject will be coded by the CRO Biometry Unit as valid or not valid for the Enrolled set, FAS, PP set and Safety set. Subjects will be evaluated according to the treatment they will actually receive (Enrolled set, FAS, PP set and Safety set).

10.1.2 Reasons for exclusion from the Full Analysis Set

Reasons for the exclusion from the Full Analysis Set are the following:

- failure to be administered the investigational product
- lack of any primary efficacy data post enrolment
- failure to satisfy major inclusion/exclusion criteria (eligibility violations). Subjects who fail to satisfy an inclusion/exclusion criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:
  - the inclusion/exclusion criterion was measured prior to enrolment
  - the detection of the relevant eligibility violations can be made completely objectively
  - all subjects receive equal scrutiny for eligibility violations (blind review)
  - all detected violations of the particular inclusion/exclusion criterion are excluded

10.1.3 Reasons for exclusion from the Per Protocol set

Reasons for the exclusion from the Per Protocol set include the following:

- lack of compliance to the IMP
- exposure to an IMP different from the one assigned to the subject
- missing primary efficacy data
- more than 20% of the actual block assessment times outside the recommended ranges (see § 7.1.4)
- failure to satisfy any inclusion/exclusion criteria (eligibility violations)
- intake of prohibited medications before the end of surgery during the first 45 min calculated from the time of readiness for surgery and not foreseen by the study protocol (see § 5.3.1 and 5.3.3) with the exception of sedation before anaesthesia, additional anaesthesia and rescue analgesia (see §5.3.2). If sedation before anaesthesia (excluding oral midazolam) or additional anaesthesia or analgesia is required before the end of surgery during the first 45 min calculated from the time of readiness for surgery, the subject will be included in the PP set and evaluated as block failure.

10.2 Sample size and power considerations

Given the following definitions:

$\boldsymbol{\pi_T}$ = Proportion of success - Test (Chloroprocaine);
$\boldsymbol{\pi_R}$ = Proportion of success - Reference (Ropivacaine);
$\boldsymbol{\epsilon = \pi_T - \pi_R}$ (difference between Test and Reference proportion of success);
$\boldsymbol{\delta}$ = Non-inferiority limit;

the sample size for the one-sided hypothesis test $\mathbf{H_0: \epsilon \leq \delta}$ vs. $\mathbf{H_a: \epsilon > \delta}$ can be computed according to the following formula (45):

$N_T = k \times N_R$ and $N_R = \text{ceiling}\ \{[(Z_{1-\alpha} + Z_{1-\beta})^2 / (\epsilon - \delta)^2] \times [\pi_T \times (1 - \pi_T)/k + \pi_R \times (1 - \pi_R)]\};$

where:

k = Balancing ratio between treatment arms (1 for balanced group)
N_T = Number of subjects included into the Per Protocol set for Test treatment group;
N_R = Number of subjects included into the Per Protocol set for Reference treatment group;

Considering a one-sided type I error **α = 0.025**, a type II error **β = 0.2**, a non-inferiority margin **δ = -0.1** and a proportion of success of **0.95** in both treatment groups, **75** patients per treatment group are required. Assuming an exclusion rate from the Per Protocol Set of **15%**, **90** patients per group will be recruited for a total number of **180** patients.

10.3 Handling of missing data

10.3.1 Methods for replacing missing data

- Multiple imputation (MI) under missing at random (MAR) assumption: multiple imputation is a general approach to the problem of missing data that aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. Missing at random (MAR) approach assumes that any systematic difference between the missing values and the observed values can be explained by differences in observed data. The use of multiple imputation under MAR assumption provides unbiased estimations of the parameters and allows evaluating the uncertainty of parameters' estimation due to the presence of missing data. Separate multiple imputations will be performed for each treatment arm.
- Missing as Failure (MF): missing values of the primary end-point are considered as block failures regardless of the treatment arm.
- Worst Case (WC): missing values of the primary end-point are considered as block failures if the patients receive Test product and as block successes if the patients receive Reference product.

10.3.2 Replacement rules for each analysis set

- Enrolled set: all missing data will not be replaced.
- Full Analysis Set (FAS): missing data of the primary end-point (if any) will be replaced according to MI under MAR assumption method, MF method and WC method in three different sensitivity analyses. Missing data of the secondary end-points will not be replaced.
- Per Protocol set (PP): no replacement of missing data is required for the primary end-point. Missing data of the secondary end-points will not be replaced.
- Safety set: all missing data will not be replaced.

10.4 Demographic, baseline and background characteristics

Critical demographic characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarised in contingency tables. Quantitative data will be summarised using classic descriptive statistics.

10.5 Analysis of efficacy parameters

The efficacy analysis will be performed on the PP set (primary efficacy analysis) and FAS (sensitivity analyses). The observed response rate for each treatment group will be calculated as the proportion of subjects with a successful block (as defined in § 9.2).

The proportion of subjects with a successful block will be compared between treatment groups by a binomial regression model, with the factors treatment and centre as fixed effects. If the binomial regression model fails to converge, a Poisson regression model with a robust error variance (sandwich estimation) will be used instead of the binomial model (46, 47). Non-inferiority of the Test in comparison with the Reference treatment will be considered proved if the lower confidence limit of the **97.5%** one-sided confidence interval of the difference between treatments is greater than the non-inferiority margin **δ = - 0.1**.

Secondary variables (time to onset of sensory block [readiness for surgery], time to onset of motor block, time to sensory and motor block regression, time to eligibility for home discharge, time to rescue anaesthesia or analgesia, time to post-surgery analgesia) will be presented using Kaplan-Meier curves and will be compared between treatment groups by log rank test. All tests on the secondary variables will be performed with a nominal two-sided type I error $\alpha = 0.05$.

10.6 Safety and tolerability evaluation

- **AEs**

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).
AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring before the first dose of IMP and not worsening after the first dose of IMP
- TEAEs: all AEs occurring or worsening after the first dose of IMP

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarised by treatment and overall. The number and percentage of subjects with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity.

- **Physical examination**

Significant findings/illnesses, reported after the start of the study and that meet the definition of an AE (see § 11), will be recorded in the subject source documents. Date of the physical examination and overall investigator's interpretation (as normal, abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) will be reported in the CRF.

- **Vital signs**

Values of vital signs will be listed and summarised by descriptive statistics.

- **Body weight**

Values of body weight will be listed and summarised by descriptive statistics.

- **ECG**

Date and time of ECG recording and overall investigator's interpretation (normal, abnormal NCS, abnormal CS) will be reported in the CRF and listed in the final clinical study report. Hard copies of the ECGs will be attached to the CRF. All clinically significant abnormalities after the screening visit will be recorded as AEs.

11 DEFINITION AND HANDLING OF AEs AND SAEs

11.1 Applicable SOPs

AEs definition, classification and management will follow the CRO SOPs, based upon applicable local and international regulations. The full SOP or an operative summary will be made available to the clinical centre.

A brief summary of AE definition, classification and management is reported below.

11.2 Definitions

- **Adverse event (AE)**

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

- **Adverse Drug Reaction (ADR)**

Any noxious and unintended response to a medicinal product (i.e. a causal relationship between a medicinal product and an AE is at least reasonably possible in the investigator's or sponsor's opinion, the relationship cannot be ruled out) resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.

- **Pre-treatment AE (PTAE)**

Any AE occurring before the first dose of a medicinal product and not worsening after the first dose. The following medical occurrences and clinical investigations are the only clinically significant events which, according to the investigator judgement, can be defined and recorded as PTAEs:

- trauma (fractures, sprains, strains, falls, domestic accidents, car accidents, etc.) occurred after the signature of the informed consent and before the first medicinal product administration
- new measurements (vital signs, ECG, laboratory parameters, etc.), performed after the signature of the informed consent and before the first medicinal product administration, which show a clinically significant worsening in comparison with a previous (baseline) measurement performed after the signature of the informed consent
- any disease diagnosed after the anamnesis recorded at visit 1 and before the first medicinal product administration
- physical and mental status changes (pre-syncope, anxiety, dizziness, fainting, etc.) occurred after the signature of the informed consent and before the first medicinal product administration

- **Treatment-emergent AE (TEAE)**

Any AE occurring or worsening after the first dose of a medicinal product

- **Serious Adverse Event (SAE)**

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event that may jeopardize the subject's health status or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are cancer, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse

- **Unexpected ADR**: an ADR the nature or severity of which is not consistent with the Reference Safety Information (RSI)

- **Reference Safety Information (RSI)**: in order to assess whether an adverse reaction is expected, the Investigator's Brochure (IB) for the test formulation and the SmPC for the reference formulation will be used.

- **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

An ADR that is both unexpected (not consistent with the RSI) and also meets the definition of a SAE.

11.3 AEs monitoring window

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: last follow-up visit/ETV

An AE occurring after the last follow-up visit/ETV and coming to knowledge of the investigator (e.g. by spontaneous reporting by study subjects) must be recorded only if it is an ADR, according to the investigator's judgment.

11.4 AEs recording

All AEs derived by spontaneous, unsolicited reports of the subjects, by observation and by routine open questioning should be collected and reported.
The following minimal information will be recorded for an AE (detailed explanation for each element is available in the SOP or in the operative summary made available to the clinical centre) in the source documents and later transcribed into the CRF:

1. Adverse Event: progressive number of the adverse event
2. Description: verbatim description of the adverse event or
   Follow-up: progressive number of follow-up of the adverse event
3. Start Date/Time: start date/time of the adverse event or
   Follow-up Date/Time: follow-up date/time of the adverse event

4. End Date/Time: end date/time of the adverse event

5. Affected Body Area: anatomical location relevant for the event

6. Whether the adverse event start before or after the first intake of the study drug or whether the adverse event has worsened or not after the first intake of the study drug

7. Last Study Drug Administration Date/Time Before Onset: if the adverse event started after the first administration of the study drug, the date/time of last administration of the study drug before the onset of the adverse event or
Last Study Drug Administration Date/Time Before Worsening: In case of treatment emergent adverse event, the date/time of the last administration of the study drug(s) before the worsening of the adverse event.

8. Investigator's opinion about the reasonable possibility of a causal relationship with the study drug.

9. Investigator's opinion about other causal relationship (e.g. non study drug, concomitant therapy, study device, etc.).

10. Severity: the severity or intensity of the event

- 1 Mild
- 2 Moderate
- 3 Severe

11. Pattern: Used to indicate the pattern of the event over time

- 1 Single Event
- 2 Continuous
- 3 Intermittent

12. Serious Adverse Event

13. Action Taken with Study Drug: describes changes to the study drug as a result of the event. It is specifically for actions taken with the study drug

- 1 Dose Not Changed
- 2 Dose Increased
- 3 Dose Reduced
- 4 Drug Interrupted (i.e. temporary stop)
- 5 Drug Withdrawn (i.e. definitive stop)
- 6 Not Applicable (e.g. drug administration not started yet or completed)
- 7 Unknown

14. Concomitant Therapy: if a concomitant therapy is given, it must be reported in the specific CRF forms

15. Study Discontinuation: if the adverse event cause the subject to be discontinued from the study

16. Other Action Taken: other actions taken as a result of the event that are unrelated to dose adjustments of study drug

17. Outcome: Outcome of the event

- 1 Recovered/Resolved
- 2 Recovered/Resolved With Sequelae
- 3 Recovering/Resolving
- 4 Not Recovered/Not Resolved
- 5 Fatal
- 6 Unknown

11.5 SAEs reporting

The investigator must report to the sponsor any SAE within 24 h of becoming aware of the event. The Investigator, within the same timeframe, should also inform the study monitor and the CRO. The investigator shall notify the competent Ethics Committee (EC) within 7 days of any SAE with lethal outcome occurred during a study. If the Investigator is initially unable to obtain all the necessary details for completing the form, he/she should in any case transmit all the available information. The Investigator should provide an appropriate follow-up of SAEs to all concerned parties.
Seriousness and causality must be assessed by the investigator. Expectedness is usually assessed by the sponsor.
If the investigator is unable to assess the causality it is recommended to adopt a conservative approach and treat the event as a suspected adverse reaction until follow-up information is available.
The sponsor may also make an assessment of causality, independent of that of the investigator. The most conservative approach should be taken when it comes to regulatory reporting. Under no circumstances should the sponsor downgrade the investigator's opinion or put the investigator under pressure to change his/her assessment. In case of disagreement, both the opinion of the investigator and the sponsor should be provided on the report.
The sponsor will evaluate the SAE expectedness on the basis of the RSI.

11.6 SUSARs management

The clock for initial expedited reporting starts as soon as the information containing the minimum reporting criteria has been received by the sponsor (day 0).
For fatal and life-threatening SUSARs the EC and Competent Authority (CA) should be informed as soon as possible and in any case within 7 days.

If the initial report is incomplete, e.g. not all the information/assessments were available, a complete report should be sent within an additional 8 days.

SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

The minimum information to be reported includes:

- Valid EudraCT number (where applicable)
- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect IMP (including active substance name, code)

- A causality assessment (a reasonable possibility of a causal relationship with the study drug can be excluded only if there is information supporting this decision, otherwise it cannot be excluded).

11.7 Other events qualified for expedited reporting

Other safety issues also qualify for expedited reporting when they might materially alter the current benefit-risk assessment of a medicinal product or would be sufficient to consider changes in the medicinal product administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g.: a fatal outcome)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- post-study SUSARs that occur after the subject has completed a clinical trial and are reported to the investigator by the subject.
- new events relating to the conduct of the trial or the development of the medicinal product likely to affect the safety of the subjects, such as :
  - a SAE which could be associated with the trial procedures and which could modify the conduct of the trial
  - a significant hazard to the subject population such as lack of efficacy of a medicinal product used for the treatment of a life-threatening disease
  - a major safety finding from a newly completed animal study (such as carcinogenicity) or from other clinical trials.

11.8 SAEs: contacts

The CRO can be contacted using the phone and fax numbers stated in this protocol or calling the mobile phone number +41.79.822.35.07 (operative 24-h/day, 365 days/year).

SAEs must be reported on SAE reporting forms and faxed to the sponsor - contact details below:

Dr. Elisabetta Donati
Fax: +41(0)91.646.85.61
Phone: +41(0)91.640.42.50
E-mail:edonati@sintetica.com

12 DATA MANAGEMENT PROCEDURES

12.1 Data collection – CRFs

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the CRFs. He must also check that the data reported in the CRFs correspond to those in the subject's source documents.
To ensure legibility, the CRFs should be filled out in English, in block capitals with a ball-point pen (not pencil, felt tip or fountain pen). Any correction to the CRFs' entries must be carried out by the investigator or a designated member of staff. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way. A single stroke must be drawn through the original entry. Corrections have to be dated and initialled. In the interest of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full, even if there are no changes from a previous examination. The investigator must provide a reasonable explanation for all missing data.
The CRFs will be completed, signed by the investigator, sent to the CRO Biometry Unit for data management procedures and finally sent to the sponsor.

12.2 Unique subject identifier

All the subjects who sign the informed consent form for the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique subject identifier consists of the sponsor study code (i.e. CHL.2/01-2014/M), the 3-digit centre number (i.e. 001, 002 or 003), the 4-digit screening number (e.g. S001, S002, etc.) and, if applicable, the 3-digit subject randomisation number (e.g. 101, 102, …, 201, 202, …, 301, 302, etc.). Study code, centre number, screening number and subject randomisation number are separated by slashes ("/"). The last 8 digits of the unique subject identifier (enrolled subjects), corresponding to the subject screening and subject randomisation numbers separated by a slash, will appear as subject identifier in the individual listings and figures of the clinical study report and will be used to identify the subjects in in-text tables or wording (if applicable).

12.3 Database management

The CRO will provide double data entry with total re-entry of data by a second data entrist and discrepancy resolution by a third individual and will update and verify the database and create the final SAS data sets. The final data file will be transferred to the sponsor in the agreed format with all the other study documentation.

12.3.1 Coding dictionaries

Medical/surgical history and underlying diseases, physical examination abnormalities and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™).
Previous and concomitant medications will be coded using the WHO Drug Dictionary Enhanced (WHODDE). Version of coding dictionaries will be stated in the study report.

13 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

The monitoring visits will be conducted by Clinical Monitor Services, Germany (centre N. 1) and Clinical Medical Service Sagl/Cross Research S.A. in Switzerland (centres N. 2 and 3).

Monitoring will comply with ICH-GCP chapter 5.18 requirements for what concerns monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures, monitoring reports.

Adequate time and availability for monitoring activities should be ensured by the investigator and key study personnel.

Data verification is required and will be done by direct comparison with source documents, always giving due consideration to data protection and medical confidentiality. In this respect the investigator will assure support to the monitor at all times.

The investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing authorised individuals to have access to all the study documentation. In addition to the monitoring activities performed by the study monitor, the sponsor could perform some quality control activities to verify the compliance with the study procedures and the ICH-GCP guidelines.

13.2 Quality Control and Quality Assurance

The CRO has implemented and maintains a Quality System that includes quality controls and audits at different study steps with written SOPs to ensure that the study is conducted in compliance with the protocol and all effective amendments, ICH-GCP, and the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOA principles (Attributable-Legible-Contemporaneous-Original-Accurate).

The clinical centres are responsible for implementing and maintaining quality assurance and a quality control system to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

The CROs and the sponsor will be responsible each one for their respective activities.

The sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

13.3 Applicable SOPs

The sponsor, the clinical centre and the CRO will follow their respective SOPs in the conduct of the respective activities, unless otherwise stated in written agreements. SOPs will be made available for review, if required.

13.4 Data access

The investigator and the CRO will ensure that all raw data records, medical records, CRFs and all other documentation that is relevant to this study will be made accessible to monitoring activities, audits, IEC review, and regulatory inspection.

13.5 Audits and inspections

The sponsor, any independent body acting on behalf of the sponsor and the CRO have the right to perform audits according to ICH-GCP responsibilities.

The study may also be inspected by regulatory authorities.

The investigators agree, by written consent to this protocol, to fully co-operate and support audits and inspections compliance checks by allowing authorised individuals to have access to all the study documentation.

14 ETHICAL CONSIDERATIONS

14.1 Ethics and Good Clinical Practice (GCP)

The study will be performed in accordance with the relevant guidelines of the Declaration of Helsinki.

The approval of the study protocol by the relevant Ethics Committees and Health Authorities will be obtained before the start of the study.

Study notification to the Competent Authorities will be performed according to the current regulations.

The present clinical study will be carried out according to the general principles of "ICH Topic E6, CPMP/ICH/135/95", July 1996 including post Step 4 errata, status September 1997 and post Step errata (linguistic corrections), July 2002.

14.2 Informed consent

Before being enrolled into the clinical study, the subjects must have expressed their consent to participate, after the investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language by the CRO and must be approved by the EC and regulatory authorities. It will include all the elements required by law according to the ICH-GCP recommendations. In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- a description of the aims of the study and how it will be organised
- the type of treatment
- any potential negative effects attributable to the study treatment
- the freedom to ask for further information at any time
- the subjects' right to withdraw from the clinical study at any time without giving reasons and without jeopardising their further course of medical treatment
- the existence of subject insurance cover and obligations following from this cover

Adequate time and opportunity to satisfy questions will be given to the subjects and the time will be recorded.

The investigator will be supplied with an adequate number of blank informed consent forms to be used. The forms will be signed and dated by both the investigator and the subject.
A copy of the signed form will be given to the subject.

If a subject is physically unable to sign the informed consent form due to the distal upper limb injury, an impartial witness should be present during the entire informed consent discussion and, after the subject has orally consented to the participation in the trial and, if capable of

doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form.

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the investigator's study file according to the regulatory requirements (see § 15.3). The investigator will allow inspection of the forms by authorised representatives of the sponsor, EC members and regulatory authorities. He will confirm, by signing and dating the forms, that informed consent has been obtained.

14.3 Insurance policy

An insurance cover has been issued in favour of the subjects participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

14.4 Withdrawal of subjects

It will be documented whether or not each subject completed the clinical study. If, for a subject, study treatment or observations are discontinued, the type of discontinuation and the primary reason for discontinuation will be recorded.

14.4.1 Discontinuation type

- **Discontinuation from data collection**: the subject discontinues from the collection of primary and secondary end-points
- **discontinuation from interventions and data collection**: the subject discontinues from the intake of the IMP(s) and from the collection of primary and secondary end-points

14.4.2 Primary reason for discontinuation

- **Adverse event**: Any significant adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 11.2.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **pregnancy**: pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol

- **study terminated by sponsor**: an indication that a clinical study was stopped by its sponsor
- **site terminated by sponsor**: an indication that a clinical site was stopped by the study sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

In case of lack of efficacy of the investigational anaesthetic, the patient will be regarded as not having had a successful block (block failure). The patient will not be discontinued from the study.

14.4.3 Discontinuation procedures

For any subject discontinuing from interventions and findings, the investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions
- arrange for alternative medical care of the withdrawn subject, if necessary
- report in the CRF date and time of the investigational product administration, and date and primary reason of study discontinuation
- record in the CRF any follow-up, if the subject is withdrawn for an AE

Discontinued subjects will not be replaced.

14.5 Study termination

The study will be considered terminated at the date of the last visit of the last subject or upon completion of any follow-up procedure described in protocol. The investigator and the sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately.

15 ADMINISTRATIVE PROCEDURES

15.1 Material supplied to the clinical centre

Beside the investigational products, the following study material will be supplied to the clinical centre:

- final version of the study protocol
- CRF for each patient plus some spare copies
- copy of the investigator's brochure (IB) relative to the test investigational product
- product information for the reference investigational product
- informed consent forms

Moreover, before the start of the study, the investigator(s) will be provided with the following documents: ICH guidelines, confidentiality agreement (if applicable), protocol amendments (if any), declaration of Helsinki, insurance statement, SAE forms, financial agreement (if applicable), confidential subject identification code list form, drug accountability forms, investigator and study staff list form.

15.2 Protocol amendments

In order to obtain interpretable results, neither the investigator nor the sponsor will alter the study conditions agreed upon and set out in this protocol. Amendments should be made by mutual agreement between the investigator and the sponsor. Any amendment must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment becomes then part of the protocol.

All amendments will be sent to the EC and concerned Competent Authorities, according to the current regulations in the EU and Switzerland.

The amendment will be applicable only when it is approved by the concerned authorities, unless the changes consist of urgent safety measures to protect study subjects.

Non substantial amendments will be notified according to the current regulations.

15.3 Study documentation and record keeping

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

The investigator must keep source documents for each subject in the study. All information on the CRFs must be traceable to these source documents, which are generally stored in the subject's medical file. The source documents should contain all demographic and medical information, including ECGs etc., and the original signed informed consent forms.

Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

The investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects including ECG tracing, insurance contracts, certificate of analysis of the IMP(s), drug accountability records, signed informed consent forms, confidential subjects identification code, CRFs, curricula vitae of the investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final study report.

The investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents.

Study documents must be retained by the investigator and the sponsor as long as needed to comply with ICH-GCP, national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

15.4 Study subjects' recruitment

Study participants will be recruited at each clinical centre among those patients attending the clinic for distal upper limb surgery of short duration. Sixty patients should be recruited at each clinical centre.

15.5 Confidentiality and data protection

By signing this protocol, the investigator and the CRO agree to keep all the information provided by the sponsor in strict confidentiality and to request similar confidentiality from his/her staff. Study documents provided by the sponsor (protocols, IB, CRFs and other materials) will be stored appropriately to ensure confidentiality. The information provided by the sponsor to the investigator and to the CRO cannot be disclosed to others without direct written authorisation from the sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Data on subjects collected on the CRFs during the study will be documented in an anonymous way (see § 12.2). If, as an exception, it becomes necessary to identify a subject for safety or regulatory reasons, the monitor, the sponsor and the investigator will be bound to keep this information confidential.

15.6 Publication policy

The sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the investigator publishing in peer reviewed journals, presenting results at scientific congresses and posting information and results on internet-based public registers and databases.

Study results will be communicated in full to the competent Health Authorities by the submission of a complete clinical study report.

As the sponsor agrees that the study results can be published by the investigator(s), the investigator agrees to submit any manuscript (abstract, publication, paper, etc.) to the sponsor before any public disclosure.
This will be done in order to ensure that clinical study results are reported in an objective, accurate and balanced manner. The sponsor reviews the proposed manuscripts, before submission, within a reasonable period of time (30-90 days in relation with the complexity of the work).

The investigator(s) will also be provided by the sponsor with the clinical study report and the results of any additional analysis, tables, figures, etc. undertaken for the purposes of the article, in order to take responsibility for the content of the publication(s).
On an exceptional basis, the sponsor may temporarily delay registration of certain data elements (e.g. compound, name, outcome, measures, etc.) to seek necessary intellectual property protection. This is because early disclosure of such data could, in some circumstances, prevent or negatively impact patentability.

16 STUDY RESPONSIBLE PERSONS

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16.2 Institutes performing the study

16.2.1 Clinical centre

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16.3 Co-ordination, data analysis & reporting

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