Study CRO-14-122 - Sponsor code CHL.1/02-2014

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

Prospective, single centre, randomised, parallel-group, observer-blind, three doses, efficacy and pharmacokinetic study

EudraCT Number: 2014-003778-17

Investigational medicinal product:	Chloroprocaine HCl 1% solution for injection (10 mg/mL), Sintetica S.A., Switzerland
Indication:	Spinal anaesthesia
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Development phase:	Phase II
Version and date:	Final version 1.0, 03OCT14

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

This document comprises 67 pages plus Appendices

PROTOCOL APPROVAL

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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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STUDY SYNOPSIS

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

Protocol number: CRO-14-122 - Sponsor code CHL.1/02-2014

Clinical phase: Phase II

Study design: Prospective, single centre, randomised, parallel-group, observer-blind, three doses, efficacy and pharmacokinetic study

Planned nr. of centres / countries: One / Italy

Investigator and centre: *Principal investigator:* Stefano Bonarelli, MD; Istituto Ortopedico Rizzoli, SC Anestesia e Terapia Intensiva post-operatoria e del dolore IOR-IRCCS, Bologna, Italy

Test investigational medicinal product (IMP; T):
Chloroprocaine HCl 1% (10 mg/mL), injectable solution, Sintetica S.A., Switzerland.
Three single doses of the investigational product will be investigated:

- D1: 30 mg chloroprocaine HCl (3 mL)
- D2: 40 mg chloroprocaine HCl (4 mL)
- D3: 50 mg chloroprocaine HCl (5 mL)

Dose regimen: Patients undergoing elective short-duration lower limb surgery will be randomised into 3 treatment groups (15 patients per group) to receive one of the 3 single doses of Chloroprocaine HCl 1%, i.e. either D1, D2 or D3, via intrathecal injection

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

End-points:
Primary end-point: To evaluate the efficacy of the three Chloroprocaine HCl 1% doses (i.e. D1, D2 and D3) in terms of time to complete regression of spinal block (i.e. end of anaesthesia)
Secondary end-points:

- To evaluate the efficacy of the three Chloroprocaine HCl 1% doses (D1, D2 and D3) in terms of Time to onset of sensory block, Time to onset of motor block, Time to readiness for surgery, Time to resolution of motor block, Time to unassisted ambulation, Time to resolution of sensory block to S1, Sensory block metameric levels during the block, Maximum level of sensory block, Time to regression of two dermatomers with respect to the maximum level of sensory block, Time to first spontaneous urine voiding, Time to administration of rescue anaesthesia or rescue analgesia, Time to first post-operative analgesia, Time to eligibility for home discharge, proportion of patients achieving an effective anaesthesia, quality of spinal block
- To assess the concentration of chloroprocaine and its metabolite 2-chloro-4-aminobenzoic acid (CABA) in plasma after administration of D1, D2 and D3
- To assess the excretion of CABA in urine (as % of the chloroprocaine administered dose)
- To investigate the safety and tolerability of the administered Chloroprocaine HCl 1% doses on the basis of the incidence of treatment-emergent adverse events, in particular transient neurological symptoms (TNS); vital signs and ECG.

Study variables:
Primary efficacy variable:
Time to regression of spinal block (i.e. end of anaesthesia; T_{ea}), defined as the time when Bromage score returns to 0 and sensitive level returns to S2.
Secondary efficacy variables:

- Time to onset of sensory block (T_{sb})
- Time to onset of motor block (T_{mb})

STUDY SYNOPSIS (cont.)

Secondary efficacy variables, continued:

- Time to readiness for surgery (T_{rs}), defined as presence of an adequate motor block (Bromage's score ≥ 2) and loss of Pinprick sensation at the required metameric level ≥ T12
- Time to resolution of motor block (Bromage score=0; T_{rmb})
- Time to unassisted deambulation (T_{ua})
- Time to resolution of sensory block to S1 (T_{S1})
- Sensory block metameric levels (assessed until resolution of sensory block to S1)
- Maximum level of sensory block (SB_{max})
- Time to maximum level of sensory block (T_{sbmax})
- Time to regression of two dermatomers with respect to the maximum level of sensory block (T_{rd})
- Time to eligibility for home discharge (T_{hd})
- Time to first spontaneous urine voiding (T_{uv})
- Time to administration of rescue anaesthesia or rescue analgesia (T_{ra})
- Time to first post-operative analgesia (T_{pa})
- Proportion of patients achieving an effective anaesthesia
- Quality of spinal block

Pharmacokinetic variables

- Plasma concentrations of chloroprocaine and CABA at baseline (i.e. before spinal puncture) and at 5, 10, 30 and 60 min after spinal puncture
- Urine excretion of CABA from spinal puncture to time of first urine voiding

Safety variables:

- Treatment-emergent adverse events throughout the study
- Incidence of transient neurologic symptoms (TNS) at 24 h and day 7 after spinal puncture (T_{sp})
- Vital signs (blood pressure [BP], heart rate [HR] and peripheral oxygen saturation [SpO_2]); ECG

Sample size:

45 male/female patients (15 patients per dose group), aged 18-80 years, scheduled for elective lower limb surgery (less than 40 min) under spinal anaesthesia.

To calculate the required study sample size, results from a previous study with spinal injection of chloroprocaine HCl 1% were taken into consideration and normal distribution of data was assumed. Sample size was calculated using n-Query Advisor 7.0. When the sample size in each of the 3 dose groups is 13, a one-way analysis of variance will have 80% power to detect at the 0.050 level a difference in time to complete spinal block regression (T_{ea}) means characterized by a variance of means, $V=\Sigma(\mu i - \mu)^2 / G$ (where G=3) of 249.962, assuming that the common standard deviation is 30.011. To be more conservative and to take into account possible deviations from normality, the sample size is increased of about 15%. Fifteen (15) patients per dose group will be enrolled.

Main selection criteria:

Inclusion criteria:

1. *Sex, age and surgery*: male/female patients, 18-80 years old, scheduled for short duration (less than 40 min) lower limb surgery requiring ≥ T12 metameric level of sensory block
2. *Body Mass Index (BMI)*: 18 - 32 kg/m^2 inclusive
3. *ASA physical status*: I-III
4. *Informed consent*: signed written informed consent before inclusion in the study
5. *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 spinal anaesthesia. History of neuromuscular diseases to the lower extremities
2. *ASA physical status*: IV-V
3. *Further anaesthesia*: patients expected to require further anaesthesia

STUDY SYNOPSIS (cont.)

Main selection criteria:
Exclusion criteria, continued:

4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients; ascertained or presumptive hypersensitivity to the ester type and major anaesthetics
5. *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 and neurological diseases, sepsis, blood coagulation disorders, severe cardiopulmonary disease, thyroid disease, diabetes or other neuropathies.
6. *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
7. *Drug, alcohol*: history of drug or alcohol abuse
8. *Blood donation*: blood donations in the 3 months before this study
9. *Pregnancy and lactation*: missing or positive pregnancy test at screening, pregnant or lactating women
10. *Chronic pain syndromes*: patients with chronic pain syndromes (taking opioids, antidepressants, anticonvulsant agents or chronic analgesic therapy)
11. *Medications*: medication known to interfere with the extent of spinal blocks for 2 weeks before the start of the study. Hormonal contraceptives for females are allowed.

Study schedule:
The study will include a screening phase (Visit 1, days -14/1), a treatment phase (anaesthesia and surgical procedure: Visit 2, day 1), a final visit (day 1/2), a follow up at 24 h (day 2) and a final follow-up at day 7±1.
Screening Phase (visit 1, day -14/1): Patients scheduled for short duration lower limb surgery 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. Routine pre-surgery assessments will be performed according to the standard procedures of the hospital. A urine pregnancy test for women will be performed. Inclusion/exclusion criteria will be verified and patients will be assigned a consecutive screening number.
The following baseline characteristics will be recorded: demography, lifestyle, physical abnormalities, body weight, height, vital signs, peripheral oxygen saturation (SpO_2), medical/surgical history and previous/concomitant medications.

Treatment Phase (visit 2, day 1): Before the anaesthesia, patients will be questioned about adverse events and concomitant medications and will be assigned a consecutive randomisation number. According to the randomisation list they will be allocated to receive one of three doses of Chloroprocaine HCl 1%.

Blood pressure, heart rate, SpO_2 and ECG (if foreseen by the hospital procedures) will be monitored at baseline and during block placement using standard monitors. Before anaesthesia, if needed, patients will be pre-medicated with os midazolam; in addition, only if needed according to the investigator's opinion, Ringer's solution (7 mL/kg) will be infused.
The anaesthetic will be administered with a Pencil point needle, 25-Gauge Whitacre spinal needle (caudocranial direction of the needle). Lumbar puncture will be performed in the lateral decubitus position (or sitting, if more appropriate) using a midline approach at the L3/L4 or L4/L5 interspaces. After the lumbar puncture and after verifying the spontaneous flow of liquor at the beginning and at the end of the procedure, two short aspirations will be done to verify the proper positioning of the needle. Barbotage must be avoided. In case of incomplete anaesthesia, sedative, analgesics or anaesthetics should be administered. Post-operative analgesia will be given to all patients, if necessary, according to the hospital standard procedures.

The physician placing the spinal block will not be further involved in patient's care and data recording. The evolution of both sensory and motor blocks, including sensory block metameric level, will be evaluated by a blinded observer every 2 min until readiness for surgery, every 5 min until the maximum level is reached (two consecutive observations with the same level of sensory block) and then every 5 min until regression of two dermatomers with respect to the maximum level of sensory block. After that, sensory and motor block assessments will be repeated every 30 min until regression of spinal block and complete regression of sensory block to S1 (if compatible with surgical procedure).
The efficacy and safety variables listed in the "Variables" section and described below will be recorded in the CRFs.

STUDY SYNOPSIS (cont.)

Study schedule, continued:
Before the block (pre-dose assessment) and during the spinal block every 10 min until the end of anaesthesia, hemodynamic variables (HR, BP, SpO_2; ECG if available) will be monitored according to the hospital standard procedures.
Blood samples for PK analysis will be collected at baseline and at 5 10, 30 and 60 min after spinal puncture. Urine will be collected at the time of spontaneous voiding.

Sensorial block will be verified by bilateral Pinprick test using a 20-G hypodermic needle and will be recorded. Pinprick sensation will be scored as being present (score 1) or absent (score 0).

Motor block will be verified using a modified Bromage scale (0=no block; 1=hip blocked; 2=hip and knee blocked; 3=hip, knee and ankle blocked).

Readiness for surgery is defined as the presence of an adequate motor block (Bromage's score ≥ 2) and loss of Pinprick sensation at the required metameric level ≥ T12.

Effective anaesthesia is defined as the presence of adequate sensory and motor blocks as defined above with adequate duration to cover surgery.
The quality of spinal block will be verified according to the need for supplementary intravenous analgesics and sedation as follows: adequate spinal block=neither sedation nor analgesics required to complete surgery; inadequate spinal block = additional anaesthesia or analgesia (e.g. 2 µg/kg mg IV bolus of fentanyl) required to complete surgery; failed spinal block = general anaesthesia required to complete surgery. Duration of surgery will also be recorded.
A detailed description of the surgical procedure and of the concomitant medication during surgery will be given in the CRF. Time to regression of spinal block (i.e. end of anaesthesia), defined as the time when Bromage score returns to 0 and sensitive perception returns to S2 will be recorded. Time when analgesia is required will be noted. The analgesic used and its dosage will be recorded.

All AEs will be reported. Particular attention will be given to the occurrence of paraesthesia, haemorrhage, headache, miction/defecation difficulties, tiredness, nausea/vomiting, vertigo. The time to unassisted ambulation and to first spontaneous urine voiding will be recorded.

Treatment Phase (Final visit, day 1/2 or early termination visit): At the end of the surgical procedure, patients will stay in the post-operative recovery room until the criteria for discharge are met according to the hospitals' standard procedures. Vital signs, ECG (if foreseen) 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. 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 Phase: 24 h (Day 2) and 6±1 days (Day 7±1) after anaesthesia and surgery, a deputy of the investigator, not aware of the treatment administered, will question patients about symptoms of TNS and unusual sensations not associated with the operation area (buttock, thigh posterior, thigh anterior, lower limb, sacrum, calves, other areas) following prepared questions.
Patients will be contacted (by telephone if they have already left the hospital) by a deputy of the investigator not aware of the treatment administered.

Data analysis:
Statistical analyses will be done using SAS® version 9.3 (TS1M1) or higher for Windows.

Definition of analysis sets:
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 anaesthetic administration. Missing values of time to complete spinal block regression (Tea) will be replaced with the highest Tea detected in the corresponding treatment group. This analysis set will be used for sensitivity analysis.
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.

STUDY SYNOPSIS (cont.)

Data analysis, continued

Definition of analysis sets, continued:

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

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

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

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

Efficacy analysis

Continuous variables will be summarised by dose group using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max) and categorical variables will be summarised by dose group using tables of frequencies.

Due to the small sample size, collected data will be compared using nonparametric tests.

T_{ea}, T_{sb}, T_{mb}, T_{rs}, T_{S1}, T_{rmb}, T_{ua}, SB_{max}, T_{sbmax}, T_{rd}, T_{hd}, T_{uv}, T_{ra} and T_{pa} will be analysed using the Kruskal-Wallis test. Pairwise comparisons between dose groups will be performed using the Wilcoxon rank-sum test. Comparisons will be performed according to the following hierarchical order:

1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison

Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary (CPMP/EWP/908/99 guideline, 19SEP02). However, if a null hypothesis of a comparison cannot be rejected all the null hypotheses of the subsequent comparisons cannot be rejected.

The proportion of patients achieving an effective anaesthesia and the quality of spinal block will be summarised by dose group using tables of frequencies.

Pharmacokinetic analysis

Data will be listed and summarised by descriptive statistics. PK analysis will be performed using Phoenix WinNonlin® version 6.3 (Pharsight Corporation).

STUDY SCHEDULE

ACTIVITIES	Screening Phase	Treatment Phase		Follow-up Phase	
Visit	**Visit 1 Days -14/1**	**Visit 2 Day 1**	**Final Visit or ETV Day1/2**	**Day 2 24 h post-surgery**	**Day 7±1 post-surgery**
Informed consent	x				
Demography and lifestyle	x				
Medical/surgical history	x				
Physical examination	x				
Previous and concomitant medication	x	x	x	x	x
Height	x				
Body weight	x				
Vital signs (blood pressure, heart rate)[1]	x	x	x		
SpO_2[1]	x	x	x		
ECG[1]		x	x		
Pregnancy test (urine)	x				
Inclusion/exclusion criteria	x	x			
Enrolment and Randomisation		x			
Os Midazolam premedication		x[2]			
Ringer's solution infusion		x[2]			
Spinal injection		x			
Surgery (< 40 min)		x			
Sensory block assessment		x[5]			
Motor block assessment		x[5]			
Blood sampling[3]		x			
Urine collection[4]		x			
TNS questionnaire				x	x
Home discharge[6]			x	x	
Adverse events monitoring	x	x	x	x	x

1. *Vital signs and SpO_2 at screening, at baseline, during the block until the end of the anaesthesia and during post-operative recovery (final visit). 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. *If needed*
3. *Blood samples for PK analysis will be collected at baseline and at 5, 10, 30 and 60 min after spinal puncture*
4. *Urine will be collected for PK analysis at the time of first spontaneous voiding*
5. *The evolution of both sensory and motor blocks, including sensory block metameric level, will be evaluated by a blinded observer every 2 min until readiness for surgery, every 5 min until the maximum level is reached (two consecutive observations with the same level of sensory block) and then every 5 min until regression of two dermatomers with respect to the maximum level of sensory block. After that, sensory and motor block assessments will be repeated every 30 min until regression of motor block and complete regression of sensory block to S1 (if compatible with surgical procedure)*
6. *Patients will be discharged on Day 1 or on a following day after the criteria for discharge, including Aldrete's scoring scale criteria, are met and according to the hospital's standard procedures. In case of discontinuation, subjects will undergo an early termination visit (ETV)*

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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
CABA	2-chloro-4-aminobenzoic acid
CDISC	Clinical Data Interchange Standards Consortium
CSF	Cerebrospinal fluid
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
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SB_{max}	Maximum level of sensory block
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Peripheral oxygen saturation
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
T_{ea}	Time to regression of spinal block (i.e. end of anaesthesia)
T_{hd}	Time to eligibility for home discharge

T_{mb}	Time to onset of motor block
T_{sbmax}	Time to maximum level of sensory block
T_{pa}	Time to first post-operative analgesia
T_{ra}	Time to administration of rescue anaesthesia or rescue analgesia
T_{rd}	Time to regression of two dermatomers with respect to the maximum level of sensory block
T_{rs}	Time to readiness for surgery
T_{S1}	Time to resolution of sensory block to S1
T_{sb}	Time to onset of sensory block
T_{ua}	Time to resolution of motor block or time to unassisted ambulation
T_{uv}	Time to first spontaneous urine voiding
TNS	Transient Neurological Symptoms
WHODDE	World Health Organisation Drug Dictionary Enhanced

1 INTRODUCTION

1.1 Background

1.1.1 Spinal anaesthesia

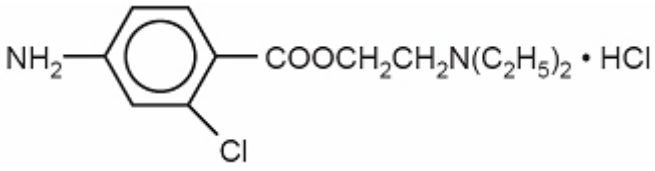
Spinal anaesthesia has the definitive advantage that profound nerve block can be produced in a part of the body by the relatively simple injection of a small amount of local anaesthetic. However, the greatest challenge of the technique is to control the spread of that local anaesthetic through the cerebrospinal fluid (CSF), to provide block that is adequate (in both extent and degree) for the proposed surgery but without producing unnecessarily extensive spread and so without increasing the risk of complications.

Spinal anaesthesia is widely used for minor procedures on the lower limb providing a fast onset and effective sensory and motor blocks.
Lidocaine was extensively used for outpatient procedures under spinal block because of its fast onset and short duration profile. However, transient neurological symptoms (TNS) were consistently reported with its use (1,2). Small doses of long-acting drugs (such as bupivacaine, levobupivacaine or ropivacaine), with or without additives, have been suggested as a possible alternative (3-6), but may be associated with an increased failure rate and with a delay in recovery (4,6).
Preservative-free solutions of chloroprocaine are also available for intrathecal use, as detailed in § 1.1.2 below.

1.1.2 Chloroprocaine HCl

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 (8,9) (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 25 seconds (27). The apparent half-life in vivo was found to be 3.1±1.6 min (range 1.5 – 6.4 min) in maternal plasma after intrapartum epidural anaesthesia (28).

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 (10), 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 (11-13). It was later demonstrated that neurological complications

were associated with the preservative agents added to chloroprocaine formulations (14). As a consequence, preservative-free and 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 (13).

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 (15,9).

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 (8,9) and related risks of toxic systemic spread (9,16,17,18).

Chloroprocaine HCl 1% solution for injection, as well as Chloroprocaine HCl 2% and 3% solutions for injection, were first approved in 1955 (NDA 009435) in the USA, under the proprietary name of Nesacaine® (AstraZeneca). The firstly developed Nesacaine® formulation contained methylparaben as preservative. Preservative-free formulations, which take advantage of chloroprocaine short duration of action, without the problematic side effects caused by the formulation excipients, were also developed.
Nesacaine 1% and 2% Injections, in multidose vials with methylparaben as preservative, are indicated for the production of local anaesthesia by infiltration and peripheral nerve block. These formulations are not to be used for lumbar or caudal epidural anaesthesia.
Nesacaine-MPF 2% and 3% Injections, in single dose vials without preservatives and without EDTA, are indicated for the production of local anaesthesia by infiltration, peripheral and central nerve block, including lumbar and caudal epidural blocks. Nesacaine and Nesacaine-MPF Injections are not to be used for subarachnoid administration. These products are marketed in USA and Canada.

Of note, in 2007 the AstraZeneca reference drug product has been withdrawn from the Swiss market. The action has been undertaken for production technical reason only, as reported by the Company, and not for safety reasons. This is also stated in the Swissmedic Journal of July 2007, where the withdrawal of the product is classified as 'Marketing Authorization revocation following the decision of the company to forgo the distribution' (Swissmedic Journal, July 2007).

Sintetica SA has registered Chloroprocaine HCl 0.5% and 1% in Switzerland. In details, Ivracain® Sintetica (Chloroprocaine HCl 0.5% Swissmedic registration n.53,283) has been authorised and marketed since 1994 for intravenous regional anaesthesia (IVRA) during upper and lower limbs surgery. Chloroprocaine HCl 1% Sintetica has been on the Swiss market since 2002 (Swissmedic registration n. 56,545) for local anaesthesia and peripheral nerve block. This formulation has been distributed locally according to Swiss law "Formula Hospitalis" since 2002 and then registered as medicinal product in 2008. Chloroprocaine HCl 1% Sintetica has also been imported by different hospitals in Belgium.

In 2012 Sintetica received approval for Chloroprocaine HCl 1% Injection, preservative-free, (complying with US Pharmacopeia) for spinal-intrathecal use under the brand name of

Ampres/Clorotekal/Decelex in several European Countries, i.e. Germany, Austria, Belgium, France, Ireland, Italy, Poland, Spain and UK.

1.1.2.1 Use of Chloroprocaine in Spinal anaesthesia

When chloroprocaine was first introduced, Foldes and McNall (10) described its use for spinal anaesthesia in 214 patients, and reported no cases of neurotoxicity. At first chloroprocaine was not extensively used for spinal anesthesia because of the wide use of lidocaine; moreover, the only solution available on the market when introduced into clinical practice contained methylparaben, a preservative, or sodium bisulfite, an antioxidant, which made them inappropriate for intrathecal use. In the '80 the literature described a number of cases with persistent neurological deficits after unintentional subarachnoid injection of large volumes of bisulfite-containing chloroprocaine resulting in total spinal anesthesia (11,12). Subsequent laboratory studies demonstrated that persistent neurologic deficits were associated with intrathecal injection of sodium bisulfite at low pH, while chloroprocaine alone did not produce irreversible neurological deficits (20,14).

Preservative-free solutions of chloroprocaine are now available for intrathecal use, as detailed above, and clinical studies in volunteers demonstrated that chloroprocaine use for spinal anesthesia at doses ranging between 30 and 60 mg provides a spinal block profile similar or even better than that of lidocaine, with a lower incidence of transient neurologic symptoms (21,22). Clinical reports on off-label intrathecal use of preservative-free chloroprocaine in more than 1000 patients (10,24,17) as well as rigorous investigations in more than 100 volunteers and outpatients (21,22,25,26) have not reported any cases of neurological toxicity.

Comparing 40 mg of either lidocaine or chloroprocaine in 8 volunteers, Kouri and Kopacz reported a similar duration of surgical block (ranging between 30 and 60 min), but faster recovery from spinal anaesthesia and simulated home discharge with chloroprocaine than lidocaine. In a prospective, randomised, double-blind study intrathecal injection of 50 mg of preservative-free chloroprocaine 1%, Sintetica SA, resulted in quicker recovery of sensory/motor function, unassisted ambulation and fewer incidences of TNS than the same dose of 1% lidocaine (26).

In a randomised, double blind clinical study by Casati A. *et al.* (26), the dose response relationship of three doses (30 mg, 40 mg or 50 mg) of Chloroprocaine HCl 1% (Sintetica SA), administered intrathecally to 45 patients (15 patients in each dose group) undergoing elective lower limb short-duration surgery, was evaluated. The onset of anaesthesia was very similar in the 3 treatment groups while supplementary intraoperatory analgesia was required in 5 and 2 patients respectively in the 30 and 40 mg group. Time to recovery of spinal block was faster in the 30 mg than in the 40 mg or 50 mg group. However, no differences in home discharge time were observed. No transient neurological symptoms were reported at 24h and 7-day follow-up. The investigators concluded that 40 and 50 mg chloroprocaine given intrathecally provide adequate spinal anaesthesia for outpatient surgical procedures of 30-60 minutes duration. Reducing the dose to 30 mg resulted in a spinal block of insufficient duration with no advantages in terms of home discharge time.

1.1.2.2 Pharmacokinetics of chloroprocaine

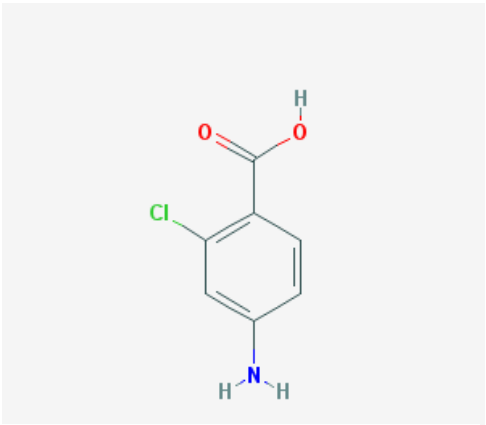
The most important clinical properties of local anaesthetic agents are potency, onset, duration of action and relative blockade of sensory and motor fibres. These qualities are related primarily to physicochemical properties of the various compounds. In general, lipid solubility determines the relative intrinsic potency of the various agents, while proteins binding influences the duration of anaesthesia. The pKa is correlated with the onset of action. The pKa of 2-chloroprocaine is 8.97.
The onset of action with 2-chloroprocaine is rapid (usually within very few minutes) for infiltration, epidural, spinal anaesthesia and peripheral blocks and the duration of action is short, depending on the route and dosage used (usually not longer than 60 minutes).

Spinal anesthesia consists in the injection of the local anesthetic solutions close to the target nerve structures, located within the subarachnoid space; consequently their effect is not dependent upon the general circulation for transport to the site of action and on the plasma concentration. Therefore, the knowledge of the pharmacokinetics of the drug is more useful for safety reason rather than for the therapeutic efficacy. If 2-chloroprocaine is injected intrathecally, its effectiveness is not conditioned by plasma concentrations that actually could affect its safety when it is administered in excessive doses or after inadvertent intravascular injection.

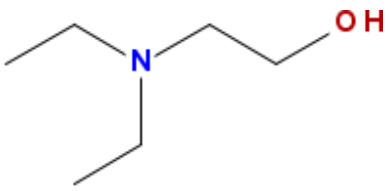
Chloroprocaine plasma half-life in vitro is about 25 seconds (27), whereas the apparent half-life in vivo was found to be 3.1±1.6 min (range 1.5 – 6.4 min) in maternal plasma after intrapartum epidural anaesthesia (28).

Chloroprocaine is in fact rapidly metabolized in the plasma by hydrolysis of the ester linkage by the enzyme pseudocholinesterase with the production of two major metabolites, i.e. β-diethylaminoethanol and 2-chloro-4-aminobenzoic acid (CABA), which inhibits the action of the sulfonamides.

Figure 1.1.2.2 Chemical structure of 2-chloroprocaine metabolites



2-chloro-4-aminobenzoic acid (CABA)



beta-diethylaminoethanol

CABA and possibly CABA conjugates (29) are eliminated through the kidney. The pharmacologically inactive hydrolytic products of 2-chloroprocaine, 2-chloroaminobenzoic acid (CABA) and 2-diethylaminoethanol, are excreted effectively in mothers and newborns (30).

Chloroprocaine may undergo some metabolism in the cerebrospinal fluid by alkaline hydrolysis, whereas pseudocholinesterase plays little role as there is almost none present in the subarachnoid space (31). At pH below 6.0 almost no alkaline hydrolysis occurs. It is conceivable that the acid pH greatly delays the hydrolysis of the drug in the cerebrospinal fluid while epinephrine prevents early uptake of the agent by the blood stream, thereby slightly delaying the usual route of elimination of the drug from the subarachnoid space.

Elimination of local anaesthetics from the cerebrospinal fluid, following intrathecal injection, occurs by diffusion and vascular absorption (32). Once in neural tissue or the epidural space, local anaesthetics are subject to vascular absorption. The predominant factors determining the rate of absorption are local blood flow and competing binding to local tissues (33). Since blood flow to the epidural space is by far greater compared with the subarachnoid space and CSF (where is approaches zero), vascular absorption in the epidural space maintains a concentration gradient between CSF and epidural space, thereby resulting in continuous elimination of local anaesthetic from the CSF after intrathecal injection (32).

Only few PK studies have been performed with local anaesthetics administered intrathecally (34-36) and some understanding comes from computational models of CSF dynamics.
To our knowledge, no studies on the pharmacokinetics of chloroprocaine or its metabolite CABA after intrathecal injection have been performed.

A study of Chloroprocaine 2 and 3% in obstetric patients after epidural anaesthesia (37) showed that in maternal plasma chloroprocaine was detectable for 5-10 min after each dose (doses: 468±284 mg for vaginal delivery and 948±347 mg for caesarean section, respectively, administered through an epidural catheter). Mean chloroprocaine levels were 51±13 (range 0-470) and 23±80 (range 0-335) ng/mL for vaginal delivery and caesarean section, respectively. In contrast, CABA was detectable at higher levels, i.e. 2±3 (0-8) µg/mL for vaginal delivery and 8±12 (1-46) µg/mL for caesarean section.

Low concentrations of chloroprocaine were detected in the venous blood of 2 out of 29 mothers at delivery after administration of 40 mL of chloroprocaine 2%. Measurable amounts of the metabolite CABA were found in all 13 samples of maternal blood 5 min after paracervical block and in 6 of 27 maternal samples at delivery (34). Similarly chloroprocaine levels of 2.7±0.7 ng/mL were found in maternal blood at delivery in another study with Chloroprocaine administered by continuous infusion (38).

It is assumed that the plasma concentrations of chloroprocaine after spinal injection are much lower than after epidural administration, also considering that approximately 10 times lower doses are administered intrathecally. In geriatric patients for example, the absorption of another local anesthetic, i.e. lidocaine 2%, after spinal injection was much lower than after epidural administration (35).

The major chloroprocaine metabolite CABA should be more easily detected after spinal anaesthesia than the parent compound, considering the results observed for epidural anaesthesia in the study described above (37).

1.2 Rationale

A previous dose-finding study, conducted as part of the development of Chloroprocaine HCl 1% Sintetica SA in spinal anaesthesia, concluded that chloroprocaine at the doses of 40 and 50 mg provide adequate spinal block for outpatient procedures lasting 45-60 min.
Chloroprocaine HCl 1%, Sintetica SA, has been approved in 2012 in Europe (PAR - Ampres 10 mg/mL solution for injection, Chloroprocaine Hydrochloride, DE/H/2866/001/DC) and is presently on the market in several European Countries under the brand name of Ampres/Clorotekal/Decelex, at the recommended doses of 40 and 50 mg, for spinal anaesthesia in adults where the planned surgical procedure should not exceed 40 min (SmPC Ampres 10 mg/10 mL).

The present prospective, randomised, blind observer study will be conducted according to the principles of Good Clinical Practice, with the same study design and procedures as the previously performed study (26), in order to confirm the efficacy of preservative-free chloroprocaine HCl 1% at the previously investigated doses. The dose of 30 mg will be further investigated in the present study, with the aim of verifying and confirming its efficacy (i.e. adequate duration of spinal block) in consideration of the approved indication in Europe and its use in the clinical practice for surgeries not exceeding 40 min. Moreover, plasma concentrations of chloroprocaine and its metabolite CABA and urinary CABA excretion will be investigated using a sensitive LC-MS/MS analytical method, to confirm the low systemic exposure to chloroprocaine following spinal injection. Drug exposure data will provide information on systemic safety of chloroprocaine HCl 1% administered intrathecally.

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 systemic adverse reactions following appropriate use of intrathecal chloroprocaine are unlikely, due to the small dose absorbed.

Chloroprocaine has been on the market under different brand names in USA and Canada for several years for the proposed indications. In addition Chloroprocaine HCl 1% Sintetica SA has been approved for the indication of spinal anaesthesia in several EU member states.

Described serious and persistent neurological complications following intrathecal administration of chloroprocaine were shown to be caused by the added preservative agents (such as sodium bisulphate and metabisulphite). No evidences exist that preservative free chloroprocaine is neurotoxic in doses appropriate for spinal anaesthesia.

The most commonly encountered acute adverse experiences are related to the central nervous system (CNS) and the cardiovascular system. These adverse experiences are generally dose related and may result from rapid absorption from the injection site, diminished tolerance, or

from unintentional intravascular injection of the local anaesthetic solution. In addition to systemic dose related toxicity, unintentional subarachnoid injection of the drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in under-ventilation or apnoea ("Total Spinal"). Factors influencing plasma protein binding, such as acidosis, systemic diseases that alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance. Plasma cholinesterase deficiency may also account for diminished tolerance to ester type local anaesthetics.

Systemic adverse reactions following appropriate use of intrathecal chloroprocaine are unlikely, due to the small dose absorbed. Systemic adverse effects of chloroprocaine are similar in nature to those observed with other local anaesthetic agents including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse.

Allergic type reactions are rare and may occur as a result of sensitivity to the local anaesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritis, erythema, angioneurotic edema (including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid type symptomatology (including severe hypotension).

2 STUDY OBJECTIVES

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

2.1 Primary end-point

The primary end-point of the study is to evaluate the efficacy of the three Chloroprocaine HCl 1% doses (30 mg [D1], 40 mg [D2] and 50 mg [D3]) in terms of time to complete regression of spinal block (T_{ea}).

2.2 Secondary end-points

The secondary study end-points are:

- To evaluate the efficacy of three Chloroprocaine HCl 1% doses (D1, D2 and D3) in terms of Time to onset of sensory block (T_{sb}), Time to onset of motor block (T_{mb}), Time to readiness for surgery (T_{rs}), Time to resolution of motor block, Time to unassisted ambulation (T_{ua}), Time to resolution of sensory block to S1 (T_{S1}), Sensory block metameric levels during the block, Maximum level of sensory block (SB_{max}), Time to maximum level of sensory block (T_{sbmax}), Time to regression of two dermatomers with respect to the maximum level of sensory block (T_{rd}), Time to first spontaneous urine voiding (T_{uv}), Time to administration of rescue anaesthesia or rescue analgesia (T_{ra}), Time to first post-operative analgesia (T_{pa}), Time to eligibility for home discharge (T_{hd}), proportion of patients achieving effective anaesthesia, quality of spinal block
- To assess the concentration of chloroprocaine and its metabolite 2-chloro-4-aminobenzoic acid (CABA) in plasma after administration of D1, D2 and D3
- To assess the excretion of the CABA in urine (as % of the administered dose)
- To investigate the safety and tolerability of the administered Chloroprocaine HCl 1% doses on the basis of treatment emergent adverse events, transient neurological symptoms (TNS), vital signs (blood pressure, heart rate and peripheral oxygen saturation [SpO_2]) check and ECG recording.

3 CLINICAL SUPPLIES

3.1 Treatment

3.1.1 Description of products

TEST (T)

IMP	Chloroprocaine HCl 1% (10 mg/mL)
Manufacturer and Supplier	Sintetica S.A., Switzerland
Pharmaceutical form	Solution for injection (5-mL ampoule)
Dose	D1: 3 mL corresponding to 30 mg chloroprocaine HCl D2: 4 mL corresponding to 40 mg chloroprocaine HCl D3: 5 mL corresponding to 50 mg chloroprocaine HCl
Administration route	Intrathecal

3.1.2 Dose regimen

Patients will be randomised to one of three treatment groups to receive Chloroprocaine HCl 1% as anaesthetic before surgery, at one of three dose levels according to the randomised, parallel-group design of the study.

In details:

- Patients in D1 group will receive a single dose of 3 mL Chloroprocaine HCl 1% (corresponding to 30 mg chloroprocaine HCl)
- Patients in D2 group will receive a single dose of 4 mL Chloroprocaine HCl 1% (corresponding to 40 mg chloroprocaine HCl)
- Patients in D3 group will receive a single dose of 5 mL Chloroprocaine HCl 1% (corresponding to 50 mg chloroprocaine HCl).

The doses are summarised in the following scheme:

Table 3.1.2.1 Dose groups

Dose group	N of patients	IMP	Dose
D1	15	Chloroprocaine HCl 1%	30 mg
D2	15		40 mg
D3	15		50 mg

The investigational product will be provided in 5-mL ampoules. The volume corresponding to the three doses to be injected in the three treatment groups (i.e. 3, 4 and 5 mL) will be taken from the ampoule using a graduated syringe. The residual amount will be collected from the ampoule using another graduated syringe, completely sealable, and retained for drug accountability together with the empty ampoule (§ 3.4).

3.1.3 Route and method of administration

Before the placement of the spinal block, according to the investigator's opinion, patients will be premedicated with os midazolam and, if needed, 7 mL/kg of Ringer's solution, according to standard medical procedures.

The investigational product Chloroprocaine HCl 1% will be administered by intrathecal injection to the patients at the three doses reported above (15 patients/dose group).

The skin area where the injection is performed will be aseptically prepared according to the routine procedure of the hospital (e.g. chlorhexidine; iodine-based disinfectants must not be used; see § 5.3.1). Before and during spinal block, vital signs (blood pressure, heart rate), SpO_2 and ECG (if foreseen by the hospital procedures) will be monitored every 10 min until the end of the anaesthesia, according to the standard procedures of the hospital.

The investigational product will be injected with a syringe provided with a 25-gauge Whitacre spinal needle (Pencil point needle). The needle hole will be oriented towards the skull (caudocranial direction of the needle).
The injection will be performed using a midline approach, at the L3/L4 or L4/L5 interspaces, with the patient in the lateral decubitus position (or sitting position if more appropriate) and the area to be operated distally located.
After the lumbar puncture and after verifying the spontaneous flow of liquor at the beginning and at the end of the procedure, two short aspirations will be done to verify the proper positioning of the needle. Barbotage must be avoided. In case of incomplete anaesthesia, sedative, analgesics or anaesthetics should be administered.

Post-operative analgesia will be given to all patients, if necessary, according to the hospital standard procedures.

3.1.4 Investigational product distribution

The investigational product will be administered by the investigator or by his/her deputy. The investigational product will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study. Since this is an observer-blind study, the physician placing the spinal block will not be further involved in patient's care and data recording.

3.2 Packaging and labelling

Packaging and labelling will be carried out by the Sponsor according to the randomisation list. The primary packaging for the investigational product will be a 5-mL glass ampoule packed in individual carton packages (patients' kits). Each patient kit will contain the glass ampoule with the IMP and a sealable graduated syringe for the collection of the residual product after administration (see § 3.1.2).

Labelling in local language 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;

3.3 Storage conditions

The test product must be stored at a temperature ≤ 25°C. The test product will be stored in a dry locked place, sheltered from light. The product will not be refrigerated or frozen.

3.4 Drug accountability

The investigational product will be provided directly to the pharmacy of the clinical site 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 delivery forms.

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

4 INVESTIGATIONAL PLAN

4.1 Overall study design

This is a prospective, single centre, randomised, parallel-group, observer-blind, three doses, efficacy and pharmacokinetic study.

4.2 Discussion of design

Several dose-finding studies in adult volunteers evaluated spinal block characteristics of chloroprocaine at different doses, supporting its potential usefulness for outpatient surgery. In a randomised, double blind investigation on the intrathecal injection of 3 doses of Chloroprocaine HCl 1% in adult patients (parallel groups), doses of 40 and 50 mg of Chloroprocaine HCl 1% (Sintetica SA) provided adequate spinal anaesthesia for lower limb elective outpatient procedures lasting <40 - 60 min (26). In that study, the 30 mg dose provided a faster regression of the spinal block compared with the 40 and 50 mg doses and in the clinical practice the 30 mg dose resulted in a spinal anaesthesia of sufficient duration for surgical procedures < 40 min.

Chloroprocaine HCl 1%, Sintetica SA, has been approved in 2012 in Europe (PAR - Ampres 10 mg/mL solution for injection, Chloroprocaine Hydrochloride, DE/H/2866/001/DC) and is presently on the market in several EU countries (see § 1.2) at the recommended doses of 40 and 50 mg, with the therapeutic indication of spinal anaesthesia in adults where the planned surgical procedure should not exceed 40 min (SmPC Ampres 10 mg/mL).
The design of the present study is based on the previously performed study (26), in order to confirm the results obtained with the doses of 40 and 50 mg and to further investigate the dose of 30 mg, with the aim of verifying and confirming its efficacy (i.e. adequate duration of spinal block) in consideration of the approved indication in Europe and its use in the clinical practice for surgeries not exceeding 40 min. In the study in fact only patients scheduled for surgical procedures of a duration < 40 min will be included.

The study is randomised to control for bias.

Due to the different volumes of the anaesthetic solution that will be used for the three doses, the study will be observer-blinded. In fact, the investigator placing the spinal block will be aware of the treatment administered. There will be no possibilities of administering the different doses in a way that will make them unrecognizable. However, the physician placing the spinal block will not be further involved in patient's care and data recording and all the study variables will be evaluated and recorded by an investigator, or his/her deputy, blinded to the dose injected.

Elimination of local anaesthetics from the cerebrospinal fluid following intrathecal injection occurs by diffusion and vascular absorption. However, only few PK studies have been performed with local anaesthetics administered intrathecally (34-36) and some understanding comes from computational models of CSF dynamics.
No studies on chloroprocaine or its metabolite plasma pharmacokinetics after intrathecal injection have been performed and studies with chloroprocaine 2 and 3% chloroprocaine in

epidural anaesthesia indicated a low plasma exposure and early disappearance of the parent drug. Plasma levels of chloroprocaine after spinal injection are expected to be negligible.

Thus, concentrations of chloroprocaine in plasma after spinal injection will be investigated in the present study at the three administered doses using a sensitive LC-MS/MS analytical method to confirm the low systemic exposure to this anaesthetic following spinal injection. Most importantly, drug exposure data will provide information on systemic safety of chloroprocaine HCl 1% administered intrathecally.

Considering the short half-life of chloroprocaine (approximately 25 sec in vitro, 2-6 min in vivo), the sampling time of 5 min post-dose has been chosen in order to try to detect the drug in plasma before its complete hydrolysis. Additional sampling times are 10, 30 min and 1 h post-dose.

In addition, the product of cholinesterase hydrolysis, i.e. the metabolite 2-chloroaminobenzoic acid (CABA), will be determined in plasma up to 1 h post-dose. Plasma levels of the metabolite should be much higher than for the parent drug, according to a previous work performed with chloroprocaine administered through an epidural catheter (37).

The metabolite will also be analysed in urine collected at the first urine voiding time, in order to evaluate chloroprocaine bioavailability in terms of percentage of metabolite product excreted in the urine in relation to the administered dose of chloroprocaine (molar ratio).

In the present study the occurrence of TNS, which have been reported after spinal anaesthesia, (see SmpC) will be carefully monitored.
In addition, for all intrathecal injections a Pencil point needle, 25 Gauge diameter, will be used in order to decrease the risk of PDPH occurrence.
It is to note, however, that no TNS were reported in previous clinical trials in adults using Sintetica Chloroprocaine HCl 1% (1,26).

Occurrence of clinically relevant hypotension (defined as a decrease in systolic arterial blood pressure by approximately 30% or more from baseline values) and bradycardia (defined as heart rate decrease below 45 beats per minute) will be monitored throughout the study and if observed appropriately treated.

Premedication with midazolam will be used for sedation in patients to reduce possible anxiety before the operation. This is common clinical practice.

5 STUDY POPULATION

5.1 Target population

Forty-five (45) male/female patients, 15/dose group, aged 18-80 years, scheduled for lower limb surgery (< 40 min) under spinal block, i.e. requiring ≥ T12 metameric level of sensory block.

5.2 Inclusion criteria

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

1. *Sex, age and surgery*: male/female patients, 18-80 years old, scheduled for short duration (less than 40 min) lower limb surgery requiring ≥ T12 metameric level of sensory block
2. *Body Mass Index (BMI)*: 18 - 32 kg/m^2 inclusive
3. *ASA physical status*: I-III
4. *Informed consent*: signed written informed consent before inclusion in the study
5. *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 spinal anaesthesia. History of neuromuscular diseases to the lower extremities
2. *ASA physical status*: IV-V
3. *Further anaesthesia*: patients expected to require further anaesthesia
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients; ascertained or presumptive hypersensitivity to the ester type and major anaesthetics
5. *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 and neurological diseases, sepsis, blood coagulation disorders, severe cardiopulmonary disease, thyroid disease, diabetes or other neuropathies
6. *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
7. *Drug, alcohol*: history of drug or alcohol abuse
8. *Blood donation*: blood donations in the 3 months before this study

9. *Pregnancy and lactation*: missing or positive pregnancy test at screening, pregnant or lactating women
10. *Chronic pain syndromes*: patients with chronic pain syndromes (taking opioids, antidepressants, anticonvulsant agents or chronic analgesic therapy)
11. *Medications*: medication known to interfere with the extent of spinal blocks for 2 weeks before the start of the study. Hormonal contraceptives for females are allowed.

5.3.1 Not allowed treatments and other treatments

No medication known to interfere with the extent of spinal block (see chloroprocaine SmPC), in particular no therapeutic use of opioids, will be allowed for 2 weeks before the start of the study and during the whole study duration. Hormonal contraceptives for women are allowed.

The area to be operated will be aseptically prepared with disinfectants, e.g. chlorhexidine, not containing iodine. Iodine-based disinfectants must not be used. The information on the iodine-free disinfectant used for each patient will be reported in the individual CRFs.

Before the placement of the spinal block, if needed, patients will be premedicated with os midazolam and, only if necessary, 7 mL/kg of Ringer's solution administered by infusion, according to the investigator's opinion.
Post-operative analgesia will be given to all patients, if necessary, according to the hospital standard procedures.

6 STUDY SCHEDULE

The schedule of the study is summarised at page 10.

6.1 Study visits and procedures

The study protocol foresees a screening visit, one study treatment for each patient, followed by post-operative recovery, final visit and 2 follow-ups. Maximum study duration will be 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 last 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
- **Treatment 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)
  - Day 2 (i.e. 24 h after surgery) - Telephonic follow-up, if the patient has left the hospital on day 1
  - Day 7±1 (6±1 days after surgery) - Telephonic follow-up

	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 and life style recording ➢ Previous/concomitant medications ➢ Routine pre-surgery assessments according to the hospital standard procedures, including medical/surgical history, physical examination, height, weight, vital signs (blood pressure, heart rate), SpO_2 ➢ Urine pregnancy test for women ➢ Inclusion/exclusion criteria evaluation ➢ AE monitoring	
Treatment - Visit 2	*Day 1*	➢ Concomitant medications ➢ Adverse events (before, during and after block placement and surgery) ➢ Inclusion/exclusion criteria evaluation ➢ Subject randomisation ➢ Vital signs, SpO_2 and ECG (if foreseen by the standard hospital procedures) ➢ Premedication: os midazolam and 7 mL/kg Ringer's solution, if needed ➢ Anaesthesia administration (intrathecal injection) ➢ Post-operative analgesia according to the hospital standard procedures ➢ Sensory and motor block assessments, including sensory block metameric level ➢ Quality of spinal block assessment ➢ Surgery (< 40 min) ➢ Blood sampling for PK analysis at pre-dose (0h) and at 5, 10, 30 and 60 min after spinal puncture ➢ Urine collection for PK analysis at the time of first urine voiding	
Final Visit/ETV	*Day 1/2 or upon discontinuation for ETV*	➢ Final assessments before discharge according to the hospital's standard procedures ➢ Aldrete's scoring scale ➢ Vital signs (BP, HR, SpO_2) and ECG (if foreseen by the standard hospital procedures) ➢ AE and concomitant medications ➢ Discharge (when criteria for discharge are met and according to the hospital's standard procedures) In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Standardised meals will be served according to the hospital 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.

	Day	Procedures/Assessments	Notes
Follow-up	*Day 2 (24 h after surgery)*	➢ AE, in particular TNS (questionnaire) ➢ concomitant medications	
Follow-up	*Day 7±1 post-surgery*	➢ AE, in particular TNS (questionnaire) ➢ concomitant medications	

6.2 Diet and lifestyle

Study participants will undergo study procedures as outpatients or in-patients, 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 on Day 1 or on a following day after meeting the criteria for discharge, according to the hospital procedures.

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, including body weight and evaluation of the physical status according to ASA general relative values, will be performed at the pre-surgery (screening) visit.

7.1.1 Vital signs

Patients' blood pressure (BP), heart rate (HR) and peripheral oxygen saturation (SpO_2) will be measured by the investigator or his/her deputy after 5 min at rest (sitting position) according to the hospital procedures.
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%

SpO_2 values < 95% but ≥ 92% will be considered not clinically significant.

Haemodynamic variables (BP, HR and SpO_2), will be recorded at screening, at baseline (before the block) then every 10 min from spinal injection until the end of the anaesthesia. Standard monitors will be used according to ASA recommendations. SpO_2 should be ≥ 92% during the monitoring period.
Blood pressure, heart rate and SpO_2 will be monitored also at post-operative recovery and final visit. To meet criteria for discharge, the patients' haemodynamic variables must be stable and SpO_2 must be acceptable (> 92%).

Screening, baseline and final/early termination assessments of haemodynamic variables and any other assessment judged clinical significant will be reported into the CRF.

Occurrence of clinically relevant hypotension (defined as a decrease in systolic arterial blood pressure by approximately 30% or more from baseline values) and bradycardia (defined as heart rate decrease below 45 beats per minute) will be monitored throughout the study and if observed appropriately treated.

7.1.2 ECGs

ECG (if foreseen by standard hospital procedures) will be monitored using standard monitors at baseline (before block placement), during the block (every 10 min) and at post-operative recovery / final visit

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

Any assessment judged as clinical significant will be reported in the CRF.

7.1.3 Assessment of adverse events

For the definition of adverse events please refer to § 11.

Adverse events will be assessed throughout the study from the signature of the informed consent up to the second follow-up (day 7±1).

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

Any complication during anaesthesia, e.g. paraesthesia and micturition disorders will be recorded.

Patients will be questioned about the occurrence of treatment-emergent adverse events (TEAEs; see § 10.6). Particular attention will be given to systemic and local toxicity symptoms, neurological symptoms and allergic reactions. The occurrence of headache and of lower limbs and gluteus paraesthesia will be carefully checked. Patients will also be instructed to report signs of systemic (central nervous system) toxicity.

Particular attention will be given to the possible occurrence of transient neurological symptoms (TNS). In particular the incidence of TNS and unusual sensations not associated to the operation area will be assessed at 24 h and day 7 after surgery through a telephonic interview (if the patient has already left the hospital). A specific questionnaire will be filled-in and the following symptoms will be questioned (see Appendix 1):

- Well being
- fatigue
- nausea/vomiting
- dizziness
- urination/defecation difficulty
- pain at the site of injection
- pain at the site of surgery
- unusual sensations (burning, tingling, dull, aching, numbness, hypoesthesia or other sensations)
- location of the symptoms (buttocks, thighs anterior, thighs posterior, lower limbs, sacrum, calves or back [one sided or bilateral])
- previous experience of such symptoms

The questionnaire will be reviewed by the investigator who will judge whether the reported symptoms could be classified as TNS on the basis of the available evidence and referring to the diagnosis criteria reported by Pollock *et al.* (15) and ASA, and summarized in the table below:

Table 7.1.3.1 Differential diagnosis criteria for TNS and other events following intrathecal injection

Event	Onset – Duration	Symptoms	Treatment
TNS	6-36 h after spinal or epidural anaesthesia/1-7 days	Unilateral or bilateral pain in the anterior or posterior thigh ± extension into legs ± back pain No motor weakness No neurological abnormalities	NSAIDs, opioids, warm heat, trigger-point injections
Epidural haematoma	0 - 2 days	Muscle weakness, radicular back pain, sensory deficit	CT scan, neurological consult, surgical decompressive laminectomy
Epidural abscess	2 - 7 days	Backache, progressive neurological symptoms ± fever	Antibiotics, possible surgical drainage
Spinal nerve injury	0 - 2 days/1 - 12 weeks	Pain during insertion of needle or catheter, pain on injection, paraesthesia, pain and numbness over distribution of nerve root	May need EMG to assess baseline neurological status
Anterior spinal artery syndrome	Immediate	Postoperative painless paraplegia	If secondary to vasospasm may respond to vasodilating drugs and hypertensive therapy
Adhesive arachnoiditis	0 months	Pain on injection, variable degree of neurological deficit, often progressive, with pain and paraplegia	Diagnosis by CT, MRI or myelography. No effective treatment
Cauda equine syndrome	0 days	Loss of bowel and bladder function, paraplegia, motor weakness, sensory loss	No effective treatment

7.2 Block assessment

The evolution of both sensory and motor blocks, including sensory block metameric level, will be evaluated by a blinded observer every 2 min until readiness for surgery, every 5 min until the maximum level is reached (two consecutive observations with the same level of sensory block) and then every 5 min until regression of two dermatomers with respect to the maximum level of sensory block. After that, the efficacy assessments will be repeated every 30 min until regression of spinal block and complete regression of sensory block to S1 (if compatible with surgical procedure).

Block assessment times should not deviate more than the recommended deviation time ranges summarised in the following table.

Table 7.2.1 Recommended maximal deviations from the scheduled block assessment times

Block assessment times	Deviation
Every 2 min until readiness for surgery	---
Every 5 min until the maximum level is reached	± 1 min
Every 5 min until regression of two dermatomers with respect to the maximum level of sensory block	± 1 min
Every 30 min until regression of spinal block and complete regression of sensory block to S1 (if compatible with surgical procedure)	± 5 min

Any deviations 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.

Sensorial block will be verified by bilateral Pinprick test using a 20-G hypodermic needle and will be recorded. Pinprick sensation will be scored as being present (score 1) or absent (score 0).

Motor block will be verified using a modified Bromage scale (0=no block; 1=hip blocked; 2=hip and knee blocked; 3=hip, knee and ankle blocked).

Readiness for surgery is defined as the presence of an adequate motor block (Bromage's score ≥ 2, T_{mb}) and loss of Pinprick sensation at the required metameric level ≥ T12 (T_{sb}).

Effective anaesthesia is defined as the presence of adequate sensory and motor blocks, as defined above, with adequate duration to cover surgery. The quality of spinal block will be verified according to the need for supplementary intravenous analgesics and sedation as follows:

- **adequate spinal block**=neither sedation nor analgesics required to complete surgery;
- **inadequate spinal block**= additional anaesthesia or analgesia (e.g. 2 µg/kg mg IV bolus of fentanyl) required to complete surgery;
- **failed spinal block** = general anaesthesia required to complete surgery.

Duration of surgery will also be recorded.

A detailed description of the surgical procedure and of the concomitant medication during surgery will be given in the CRF. Time of end of anaesthesia (complete regression of spinal block), defined as the time when Bromage score returns to 0 (resolution of motor block) and sensitive perception returns to S2 will be recorded on the CRF.
Time when analgesia is required will be noted. The analgesic used and its dosage will be recorded in the CRF.
The time to unassisted ambulation and to first urine voiding will be recorded.

7.3 Procedures for discharge

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 ≥ 18 on the modified Aldrete's scoring scale (39,40; Appendix 2). 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 gluteus and of the lower limb, 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.

7.4 Sampling for pharmacokinetic analysis

7.4.1 Venous blood sampling

Venous blood samples (8 mL) for PK analysis will be collected from a forearm vein at the following times:

- Before spinal puncture (pre-dose, 0 h), 5, 10, 30 and 60 min post-dose

Actual sampling times for each subject will be recorded in the individual case report forms (CRFs).
Deviations in actual sampling times should not exceed the recommended ranges reported in the following table. Any deviations outside the recommended ranges will be verified through Data Clarification Forms and will not automatically lead to the exclusion of the concerned subjects from the PK Sets.

Table 7.4.1.1 Recommended maximal deviations from the scheduled sampling times

Sampling time	Deviation
Pre-dose (0)	Within 60 minutes before IMP administration
5 min, 10 min	0 min
30 min	± 1 min
60 min	± 3 min

Blood samples for PK analysis will be collected using an indwelling catheter with switch valve or by direct venipuncture. If using the catheter, if feasible, the cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution containing 20 I.U./mL Na-heparin. The first 2 mL of blood will be discarded at each collection time to avoid contamination of the sample with heparin.
Six (6) mL of blood will be either directly collected or transferred from the catheter with a syringe into heparinised tubes (Li-heparin) containing an esterase inhibitor. The tubes will be gently inverted for 10 times and then put on ice. Then, within 15 min from collection, the samples will be centrifuged at 4° C for 10 min at 2000xg to obtain plasma. Each plasma sample will be immediately divided into two aliquots of 1 mL each, P1 and P2, in pre-labelled polypropylene tubes, and stored frozen at ≤-70° C until analyses.

7.4.2 Urine collection

Bladder must be emptied before the anaesthetic injection, if possible.

Urine for PK analysis will be collected at the time of first urine voiding.

The urine will be collected into containers, urine volume will be measured and after thorough mixing two aliquots of 10 mL each (U1 and U2) will be prepared in polypropylene tubes. The two aliquots will be stored at ≤-70° C until analyses.
If the collected urine cannot be immediately processed, the complete sample will be kept refrigerated at approximately 4° C before measurement of volume and aliquots preparation.

7.4.3 Analytics

The concentration of chloroprocaine and its metabolite CABA in plasma and of CABA in urine will be determined at Accelera Srl, Italy, using a fully validated LC-MS/MS method. The lower quantification limit (LQL) will be specified in the validation report and analytical plan.
Analyses will be performed according to the general Principles of "OECD Good Laboratory Practices for testing of chemicals" C(81) 30 (final) and to the FDA guideline for the validation of bioanalytical methods.
The method validation report, the analytical plan and the analytical report will be attached to the final report.

7.4.4 Labelling, storage and transport of samples

7.4.4.1 Samples labelling

Each sample tube will be clearly and unequivocally identified with a label resistant to the storage temperature and reporting:

Study code	Study CRO-14-122 - Sponsor code CHL.1/02-2014
Subject number	1-45
Tube identification	P1/P2, U1/U2
Scheduled sampling time	as h; see § 7.4.1

7.4.4.2 Samples storage and transport

During the study the samples will be stored at ≤-70° C.

All aliquots 1, packed in sufficient solid CO_2, will be shipped by an authorised courier from the clinical site (Istituto Ortopedico Rizzoli, Bologna), Italy to the analytical laboratory, Accelera, Italy. Aliquots 1 will remain stored at the analytical laboratory for a maximum time of 6 months. Afterwards, the samples will be destroyed and a certificate of destruction will be provided to the sponsor.
The counter-samples (aliquots 2) will remain stored either at the analytical laboratory or at the clinical site. These samples could either be:

- sent to the laboratory for reanalysis should this become necessary for analytical reasons or if any problems occur during the delivery of aliquots 1, or

- destroyed at an authorised site, or
- transferred to the sponsor upon written request, or
- stored at the clinical site, for a maximum time of 5 years

No analyses different from those stated in this protocol and agreed by the subjects when signing the informed consent form will be performed unless a new informed consent and a new approval from the Ethical Committee is obtained. The subjects may ask to destroy their own samples at any time.

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) (41) 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.

8.2 Treatment allocation

Patients will be allocated to D1, D2 or D3 dose group in a 1:1:1 ratio according to the study randomisation list.

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

The 5-mL ampoules with the investigational product will be numbered. Each patient will be allocated the product ampoule corresponding to his/her randomisation number.

8.3 Blinding

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

The physician preparing and the physician administering the doses will not be involved in data recording and 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 centre. 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 centre 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.

9 EVALUATION PARAMETERS

9.1 Study variables

9.1.1 Primary variable

Time to regression of spinal block (T_{ea}), defined as the time when Bromage score returns to 0 and sensitive perception returns to S2.

9.1.2 Secondary variables

Efficacy variables:

- Time to onset of sensory block (T_{sb}),
- Time to onset of motor block (T_{mb}),
- Time to readiness for surgery (T_{rs}), defined as loss of pinprick sensation at the required metameric level ≥ T12 with a modified Bromage score ≥ 2,
- Time to resolution of motor block (Bromage score = 0; T_{rmb}),
- Time to unassisted deambulation (T_{ua}),
- Time to resolution of sensory block to S1 (T_{S1}),
- Sensory block metameric level (assessed until resolution of sensory block to S1)
- Maximum level of sensory block (SB_{max}),
- Time to maximum level of sensory block (T_{sbmax})
- Time to regression of two dermatomers with respect to the maximum level of sensory block (T_{rd}),
- Time to eligibility for home discharge (T_{hd}),
- Time to first spontaneous urine voiding (T_{uv}),
- Time to administration of rescue anaesthesia or rescue analgesia (T_{ra}),
- Time to first post-operative analgesia (T_{pa}),
- Proportion of patients achieving an effective anaesthesia,
- Quality of spinal block.

Pharmacokinetic variables

- Plasma concentrations of chloroprocaine and CABA at baseline (i.e. before spinal puncture) and at 5, 10, 30 and 60 min after spinal puncture
- Urine excretion of CABA from spinal puncture to time of first urine voiding

Safety variables:

- Treatment-emergent adverse events throughout the study,
- Incidence of TNS at 24 h and day 7 after spinal puncture (Tsp),

- Vital signs (BP, HR and SpO_2); ECG.

9.2 Efficacy assessments

Sensory and motor block assessment procedures and evaluations are detailed in § 7.2.

Efficacy assessments are based on the following variables:

Parameter	Description
Time to onset of sensory block (min) (T_{sb})	Time period from spinal injection (T_{sp}; time 0 h) to achievement of sensory block (as defined in § 7.2).
Time to onset of motor block (min) (T_{mb})	Time period from spinal injection (T_{sp}; time 0 h) to achievement of motor block (as defined in § 7.2).
Time to readiness for surgery (min) (T_{rs})	Time period from completion of spinal injection (T_{sp}; time 0 h) to achievement of sensory and motor block adequate for surgery, i.e. loss of Pinprick sensation and Bromage's score ≥ 2 at the required metameric level ≥ T12
Time to regression of spinal block (min) (T_{ea})	Time period from spinal injection (T_{sp}; time 0 h) to the time when the Bromage score returns to 0 and sensitive perception returns to S2
Time to resolution of sensory block to S1(min) (T_{S1})	Time period from spinal injection (T_{sp}; time 0 h) to the time when sensitive perception has returned to S1
Time to resolution of motor block	Time period from spinal injection (T_{sp}; time 0 h) to the time when the Bromage score has returned to 0
Time to unassisted ambulation (T_{ua})	Time period from spinal injection (T_{sp}; time 0 h) to the time when the patient can walk unassisted
Sensory block metameric level	Metameric level of sensory block assessed from spinal injection (T_{sp}; time 0 h) until regression of sensory block to S1
Maximum level of sensory block (SB_{max})	Maximum metameric level of sensory block (decreased or absent sensation) achieved
Time to maximum level of sensory block (T_{sbmax})	Time period from spinal injection (Tsp; time 0 h) to the time when the maximum metameric level of sensory block is achieved (consider the time of the first of the two consecutive observations with the same level of sensory block)
Time to regression of two dermatomers with respect to the maximum level of sensory block (T_{rd})	Time period from spinal injection (T_{sp}; time 0 h) to the time when the sensory block decrease of two dermatomers with respect to the maximum level of sensory block
Time to eligibility for home discharge (T_{hd})	Time period from spinal injection (T_{sp}; time 0 h) to the time when the criteria from discharge are met, even if according to the hospital procedures the patient is discharged at a later time

Time to first spontaneous urine voiding (T_{uv})	Time period from spinal injection (T_{sp}; time 0 h) to the first time when the patient can pass urine unassisted
Time (h) to administration of rescue anaesthesia or rescue analgesia (T_{ra})	Time from spinal injection(T_{sp}; time 0 h) to administration of first rescue anaesthesia or analgesia (if applicable)
Time (h) to first post-operative analgesia (T_{pa})	Time from spinal injection (T_{sp}; time 0 h) to first post-operative analgesia

9.3 Pharmacokinetic assessments

- Plasma concentrations of chloroprocaine at pre-dose and at 5, 10, 30 and 60 min after spinal puncture for the three dose levels (D1, D2 and D3)
- Plasma concentrations of CABA at pre-dose and at 5, 10, 30 and 60 min after spinal puncture for the three dose levels (D1, D2 and D3)
- Urinary excretion of CABA, as percentage of administered chloroprocaine dose for the three dose levels (D1, D2 and D3)

9.4 Safety assessments

Safety and general tolerability of the investigational anaesthetic will be based on TEAEs, TNS, physical examinations, vital signs and ECG.

In particular, ECG (if foreseen by the standard hospital procedures), blood pressure, heart rate and SpO_2 will be monitored as detailed in § 7.1.1 and 7.1.2.

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 TNS symptoms. Further details on the AE assessments are given in § 7.1.3.

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) (41) 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 respects 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 treatment phase of the study. The enrolment will be performed through randomised allocation to a dose group.

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

- 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. Missing values of time to complete spinal block regression (T_{ea}) will be replaced with the highest T_{ea} detected in the corresponding treatment group. This analysis set will be used for sensitivity analysis.
- 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.
- PK Set 1 (PK 1): the PK set 1 will include all randomised patients who fulfil the study protocol requirements in terms of anaesthetic administration and have at least one post-dose blood PK sample collected.
- PK Set 2 (PK 2): the PK set 2 will include all randomised patients who fulfil the study protocol requirements in terms of anaesthetic administration and have the urine for PK analysis collected.
- Safety set: all patients who receive at least one dose of the investigational medicinal product. 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, PK set 1, PK set 2 and Safety set. Subjects will be evaluated according to the treatment they actually receive (Enrolled set, FAS, PP set, PK set 1, PK set 2 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 § 7.2)
- failure to satisfy any inclusion/exclusion criteria (eligibility violations)

10.1.4 Reasons for exclusion from the PK sets

Reasons for the exclusion from the PK sets include the following:

- lack of compliance to the IMP
- exposure to an IMP different from the one assigned to the subject
- missing of any post-dose blood sample (PK set 1)
- missing of urine collection for PK analysis (PK set 2)
- failure to satisfy any inclusion/exclusion criteria (eligibility violations)

10.2 Sample size and power considerations

To calculate the required study sample size, results from a previous study with spinal injection of Chloroprocaine HCl 1% (26) were taken into consideration and normal distribution of data was assumed. Sample size was calculated using n-Query Advisor 7.0. When the sample size in each of the 3 dose groups is 13, a one-way analysis of variance will have 80% power to detect at the 0.050 level a difference in time to complete spinal block regression (T_{ea}) means characterized by a variance of means, $V=\Sigma(\mu i - \mu)^2 / G$ (where G=3) of 249.962, assuming that the common standard deviation is 30.011. To be more conservative and to take into account possible deviations from normality, the sample size is increased of about 15%. Fifteen (15) patients per dose group have to be enrolled.

10.3 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.

10.4 Analysis of efficacy parameters

Continuous variables will be summarised by dose level groups using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max) and categorical variables will be summarised by dose level groups using tables of frequencies.

Due to the small sample size, collected data will be compared using nonparametric tests. T_{ea}, T_{sb}, T_{mb}, T_{rs}, T_{S1}, T_{rmb}, T_{ua}, SB_{max}, T_{sbmax}, T_{rd}, T_{hd}, T_{uv}, T_{ra} and T_{pa} will be analysed using the Kruskal-Wallis test. Pairwise comparisons between dose level groups will be performed using the Wilcoxon rank-sum test. Comparisons will be performed according to the following hierarchical order:

1. Overall comparison
2. D1 (30 mg) vs. D3 (50 mg) comparison
3. D2 (40 mg) vs. D3 (50 mg) comparison
4. D1 (30 mg) vs. D2 (40 mg) comparison

Due to the hierarchical testing procedure, no formal adjustment of the alpha level is necessary (42). However, if a null hypothesis of a comparison cannot be rejected, all the null hypotheses of the subsequent comparisons cannot be rejected.

The proportion of patients achieving an effective anaesthesia and the quality of spinal block will be summarised by dose level groups using tables of frequencies.

10.5 Analysis of pharmacokinetic parameters

A descriptive PK will be presented. The results will be displayed and summarised in tables and figures. Individual and mean curves (+SD at sampling times), indicating inter-subject variability, will be plotted. Data below the lower quantification limit (BLQL) will be

considered as 0 in the calculations and presented as BLQL in listings and tables. As a consequence of BLQL (i.e. 0) values, calculated geometric means (if requested) could be null. For this reason, in the presence of any null value, the geometric mean will be reported as not calculated (NC). PK analysis will be performed using Phoenix WinNonlin® version 6.3 (Pharsight Corporation).

Urinary excretion of CABA will be calculated as the amount of metabolite excreted as a percentage of the administered dose (molar ratio).

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. Overall investigator's interpretation (as normal, abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) will be reported in the CRF.

- **Vital signs**

Screening, baseline and final/early termination assessments of haemodynamic variables and any other assessment judged clinical significant will be reported into the CRF and listed in the clinical study report.
Screening, baseline and final/early termination values of vital signs will be summarised by descriptive statistics.

- **Body weight**

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

- **ECG**

Any ECG assessment judged clinical significant will be reported into the CRF.
Date and time of ECG recording, overall investigator's interpretation (as normal, abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) and HR, PR, QRS and QT parameters will be reported in the CRF and listed in the 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.

- **Incidence of TNS at 24 h and day 7 after spinal puncture (T_{sp})**

The incidence of TNS at 24 h and day 7 after spinal puncture (T_{sp}) will be summarised by dose level groups using tables of frequency.

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)**

A PTAE is 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)**

TEAE are defined as 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 and SmPC (IB) of the investigational product 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

SAEs must be reported on SAE reporting forms and faxed WITHIN 24 H to the sponsor - contact details below:

Dr. Elisabetta Donati
Fax: +41(0)91.646.85.61
Phone: +41(0)91.640.42.50
Email: 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.1/2-2014), the 3-digit centre number (i.e. 001), the 4-digit screening number (e.g. S001, S002, etc.) and, if applicable, the 3-digit subject randomisation number (i.e. 001, 002, …, 045). 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 Medical Service.

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 centre is 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 CRO 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 involved parties will conduct the present clinical study according to the declaration of Helsinki, the general principles of "ICH Topic E6, CPMP/ICH/135/95" (ICH-GCP), July 1996 including post Step 4 errata, status September 1997 and post Step errata (linguistic corrections), July 2002; Italian Ministerial Decree 15JUL97, Italian Legislative Decree 24JUN03 n. 211, Italian Legislative Decree 30JUN03 n. 196 and subsequent modifications and supplements, Guideline of the Italian Data Protection Authority for the protection of personal data of 24JUL08 – and according to the methods and the criteria described and specified in the present protocol, agreed by the principal investigator and in any case according to the current law.

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.

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
- **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 achieved an effective anaesthesia and rescue anaesthesia will be administered. 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 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 Authority, according to the current regulations in the EU.

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 the clinical centre among those patients attending the clinic for lower limb surgery of short duration. Forty-five patients should be recruited.

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. At least 30 days before submitting a written publication or presenting the study results, e.g. as part of a written or oral presentation at a conference, the investigator will submit to the Sponsor a final version of the document or article.

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.
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).
The sponsor, within 30 days of the final manuscript/presentation, may ask for a delay in the publication or presentation of the data. This is because early disclosure of such data could, in some circumstances, prevent or negatively impact patentability.

16 STUDY RESPONSIBLE PERSONS

16.1 Sponsor

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Sponsor representatives

Clinical Project Leader
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Fax: +41.91.605.1559
Email: ccamponovo@arsmedica.ch

16.2 Institutes performing the study

16.2.1 Clinical centre

Istituto Ortopedico Rizzoli, SC Anestesia e Terapia Intensiva
post-operatoria e del dolore IOR-IRCCS,
via G.C. Pupilli 1 - 40136 Bologna, Italia
Phone: +39.051.6366356
Fax: +39.051.6366647

Principal investigator
Stefano Bonarelli, MD
Email: stefano.bonarelli@ior.it

16.2.2 Drug assay

Accelera s.r.l., Viale Pasteur 10, 20014 Nerviano, Italy
Phone: +39.0331.1984.444
Fax: +39.0331.1984.200

Head of Bioanalytical laboratory
Enrico Frigerio
Email: enrico.frigerio@accelera.org

Analytical facilities and procedures were in compliance with GLP regulations.

16.3 Co-ordination, data analysis & reporting

CROSS S.A., Switzerland, and its affiliated companies CROSS Research S.A. and CROSS Metrics S.A., sharing the same quality systems, SOPs, standards and procedures.

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16.4 Monitoring

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17 REFERENCES

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18 APPENDICES

Appendix 1 TNS questionnaire

Hospital_____ Patient number:_____

Post Operative Survey 24 H After Surgery

Sex ☐ Male ☐ Female

Are you feeling good? ☐ Yes ☐ No

If NO, what are your problems? ☐ Fatigue ☐ Nausea/Vomiting ☐ Dizziness ☐ Difficulty urinating or defecating

Pain at the site of injection? ☐ Yes ☐ No

If YES, if 0 is no pain and 10 is the worst imaginable, how would you rate your average pain in the first 24 h after surgery?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
0 1 2 3 4 5 6 7 8 9 10

Pain at the site of surgery? ☐ Yes ☐ No

If YES, if 0 is no pain and 10 is the worst imaginable, how would you rate your average pain in the first 24 h after surgery?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
0 1 2 3 4 5 6 7 8 9 10

Unusual sensations? ☐ Yes ☐ No

If YES, Characteristic of these sensations: ☐ Burning ☐ Tingling ☐ Dull ☐ Aching ☐ Numbness ☐ Hypoesthesia ☐ Others_____

Location of these symptoms: ☐ Buttocks ☐ Thighs anterior ☐ Thighs posterior ☐ Lower limbs ☐ One sided ☐ Bilateral ☐ Sacrum ☐ Calves ☐ Back

Have you ever experienced such symptoms in your life before? ☐ Yes ☐ No

Date:_____ Investigator's Signature:_____

Hospital_____ Patient number:_____

Post Operative Survey 7 Days After Surgery

Sex ☐ Male ☐ Female

Are you feeling good? ☐ Yes ☐ No

If NO, what are your problems? ☐ Fatigue ☐ Nausea/Vomiting ☐ Dizziness ☐ Difficulty urinating or defecating

Pain at the site of injection? ☐ Yes ☐ No

If YES, if 0 is no pain and 10 is the worst imaginable, how would you rate your average pain in the first 24 h after surgery?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
0 1 2 3 4 5 6 7 8 9 10

Pain at the site of surgery? ☐ Yes ☐ No

If YES, if 0 is no pain and 10 is the worst imaginable, how would you rate your average pain in the first 24 h after surgery?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
0 1 2 3 4 5 6 7 8 9 10

Unusual sensations? ☐ Yes ☐ No

If YES, Characteristic of these sensations: ☐ Burning ☐ Tingling ☐ Dull ☐ Aching ☐ Numbness ☐ Hypoesthesia ☐ Others_____

Location of these symptoms: ☐ Buttocks ☐ Thighs anterior ☐ Thighs posterior ☐ Lower limbs ☐ One sided ☐ Bilateral ☐ Sacrum ☐ Calves ☐ Back

Have you ever experienced such symptoms in your life before? ☐ Yes ☐ No

Date:_____ Investigator's Signature:_____

Appendix 2 Modified Aldrete score scale

Hospital_____ Patient number:_____

Modified Aldrete's score scale		
Response	**Score**	
Able to move 4 extremities voluntarily or on command	2	
Able to move 2 extremities voluntarily or on command	1	Activity
Unable to move extremities voluntarily or on command	0	
Able to breathe deeply and cough freely	2	
Dyspnea, limited breathing or tachypnea	1	Respiration
Apneic or on mechanical ventilator	0	
Blood pressure ± 20% of pre-anaesthetic level	2	
Blood pressure ± 20% to 49% of pre-anaesthetic level	1	Circulation
Blood pressure ± 50% of pre-anaesthetic level	0	
Fully awake	2	
Arousable on calling	1	Consciusness
Not responding	0	
Able to maintain O_2 saturation >92% on room air	2	
Needs O_2 to maintain O_2 saturation >90%	1	O_2 saturation
O_2 saturation < 90% even with O_2 supplement	0	
Dry and clean	2	
Wet but stationary or marked	1	Dressing
Growing area of wetness	0	
Pain free	2	
Mild pain handled by oral medication	1	Pain
Severe pain requiring parenteral medication	0	
Able to stand up and walk straight*	2	
Vertigo when erect	1	Ambulation
Dizziness when supine	0	
Able to drink fluids	2	
Nauseated	1	Fasting-feeding
Nausea and vomiting	0	
Has voided	2	
Unable to void but comfortable	1	Urine output
Unable to void and un comfortable	0	
*May be substituted by Romberg's test, or picking up 12 clips in one hand *From: Aldrete JA. The Post-Anesthesia recovery score revisited. J Clin Anesth 1995; 7:89-91*		

Date:_____ Investigator's Signature:_____