CLINICAL STUDY PROTOCOL

STUDY TITLE:

Randomized, multi-center, double-blind, two-armed, parallel active groups, prospective trial, to evaluate, in pediatric population undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, the efficacy and safety of chloroprocaine 1% and 2% for peripheral nerve block based on concentration–response relationships.

EudraCT Number: **2018-000656-18**

Test Product:
Chloroprocaine HCl 1% injection (10 mg/mL), Sintetica S.A., Switzerland
Chloroprocaine HCl 2% injection (20 mg/mL), Sintetica S.A., Switzerland

Sponsor: SINTETICA SA, Via Penate 5, 6850 Mendrisio (Switzerland)

Clinical Phase: Phase II

Protocol Version Date:Final Version 1.0, 14June2018

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This clinical study will be conducted in accordance with the sponsor's Standard OperatingProcedures (SOPs), current Good Clinical Practice (GCP), the provisions of ICH(International Conference on Harmonisation) Guidelines and EU Directives

CONFIDENTIAL
The information in this document is considered privileged and confidential, and may not bedisclosed to others except to the extent necessary to obtain Institutional Review Board/EthicsCommittee approval, informed consent and the approval of local regulatory authorities asrequired by local law.

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List of abbreviations

AE	Adverse Event
ASA	American Society of Anesthesiologists
CI	Confidence Interval
EC	Ethics Committee
ECG	Electrocardiogram
e-CRF	Electronic Case Report Form
FLACC	Face, Legs, Activity, Crying and Consolability
GA	General Anesthesia
HCl	Hydrochloride
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IVRA	Intravenous Regional Anaesthesia
LA	Local Anesthetic
LAST	Local Anaesthetic Systemic Toxicity
LLT	Low Level Term
MedDRA	Medical Dictionary for Regulatory Activities
PNB	Peripheral Nerve Block
RA	Regional Anesthesia
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
USA	United States of America

1. PROTOCOL SYNOPSIS

Title of the study: Randomized, multi-center, double-blind, two-armed, parallel active groups, prospective trial, to evaluate, in pediatric population undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, the efficacy and safety of chloroprocaine 1% and 2% for peripheral nerve block (PNB) based on concentration–response relationships.	
EudraCT number: 2018-000656-18	**Protocol code:** CHL.2/04-2015
Sponsor: SINTETICA SA, Via Penate 5, 6850 Mendrisio, Switzerland	
Study center(s): A total number of 7 clinical sites spread across Italy (5) and Spain (2) will take part in the trial. The coordinating site site will be in Italy. All details about the recruiting centers are reported in the comprehensive list provided separately from the present document	
Planned study period: June 2018– July 2020(Recruitment period: 24 months)	**Phase of Development:** Phase II
Name of Investigational Product: Chloroprocaine HCl 1% injection and Chloroprocaine HCl 2% injection	
Name of Active Ingredient: Chloroprocaine Hydrochloride	
Indication: Local anaesthesia by peripheral nerve block (PNB)	
Background and Rationale: **The present protocol is part of an extensive Pediatric Investigational Plan (PIP) which has been submitted to the Paediatric Committee (PDCO) of the European Medicine Agency (EMA)in the contest of the marketing authorization application of chloroprocaine use for perineural block. The PDCO has adopted a positive opinion on both the PIP and the present clinical protocol.** Chloroprocaine Hydrochloride 1% Sintetica is currently marketed in 9 European countries as intrathecal (spinal) anesthetic in adults where the planned surgical procedure is not expected to exceed 40 minutes. Since 2015, the Marketing Authorization in Switzerland has been extended to chloroprocaine HCl 20 mg/mL and 30 mg/mL solutions for injection, for local anesthesia by infiltration, for PNB and epidural block, respectively. Regional analgesia, and specifically PNB, is an acceptable means of providing intraoperative anesthesia and postoperative analgesia in neonates, infants, and children while decreasing the use of systemic opioids and avoiding opioid-related adverse effects. With the advent of ultrasound and improvements in equipment in the last decade, the utilization of PNB in children has increased tremendously. Calcaneo stop and inguinal hernia repair have been considered the ideal surgeries for testing the clinical efficacy and safety of chloroprocaine since they are short procedures with low postoperative pain that only require a short- to intermediate-acting agent.	
Objectives: **Primary Objective** The primary objective of the study is the assessment of the efficacy of chloroprocaine 1% and 2%, administered by perineural, ultrasound-guided, injection in pediatric population for a successful peripheral nerve block (same volume ml/Kg) in terms of proportions of subjects not requiring rescue anesthesia during surgery.	

Secondary Objectives

Efficacy:

- time to onset of sensory block starting from completion of the Investigational Medicinal Products IMPs injection (corresponding to readiness for surgery), detected by pin-prick in case of Inguinal hernia repair (ileogastric/ileoinguinal nerve block).The response to pinprick in sedated patient will be associated to at least a 20% increase from baseline in heart rate (HR). The sensory block onset will be achieved if no apparent hemodynamic reaction to pinprick will be seen (defined as an increase in heart rate in excess of 20% compared with baseline levels), meaning that the patient is ready for surgery.
- time to onset of sensory block starting from completion of the IMPs injection (corresponding to readiness for surgery), detected by pin-prick test, in case of 'calcaneo stop' (sciatic nerve block). The response to pinprick in sedated patient will be associated to at least a 20% increase from baseline in heart rate (HR). The sensory block onset will be achieved if no apparent hemodynamic reaction to pinprick will be seen (defined as an increase in heart rate in excess of 20% compared with baseline levels), meaning that the patient is ready for surgery.
- time to regression of motor block (sciatic nerve block) by standard Bromage scale, at the start of patient's awakening, in case of calcaneo stop procedure. This phase will have to be monitored with particular care since events of agitation followed by numbness are very common in children after sevoflurane anesthesia.
- pain intensity, assessed five times in the first 3 hours after the end of surgery and during the home discharge visit (V2). Post-surgery assessment will be performed immediately at awakening and 30 minutes, 1 hour, 2 hours and 3 hours after this first evaluation. The following tools will be used for pain evaluation: COMFORT scale for patients <2 months of age, FLACC scale for patients aged ≥ 2 months ≤ 6 years, and Wong-Baker scale for patients over 6 years of age, respectively;
- Time to eligibility for home discharge defined as: "the time elapsed from completion of surgery to the time when criteria for discharge are met, regardless if the patient will be discharged from the hospital at a later time, according to the hospital procedures". The criteria for discharge will be defined according with the Pediatric Post Anesthesia Discharge Scoring System (Ped-PADSS)
- if rescue anaesthesia (fentanyl) was required during both surgical procedures performed;
- time and dosage of rescue anaesthesia (fentanyl) required during surgery, in addition to IMPsinjection;

Safety:

The secondary, safety objectives of the trial will be to assess:

- the general tolerability and safety of the study drug, assessed through summaries of adverse events;
- pain at injection site, neurological symptoms (such as: convulsions) and cardiac symptoms (such as bradycardia and heart failure etc.) evaluated during surgery after IMP injection.

Study design:

This is a prospective, randomized, multicenter, double blind, parallel active groups, concentration-response model in pediatric population since birth to <18 years of age, phase II clinical trial.The study consists of a treatment period of 1 day and of a single perineural injection, administered through ultrasound-guided technique in order to avoid the risk of chloroprocaine IV injection.

Planned number of patients:

A total of 174 (87 per treatment group, allocated to 1% or 2% arm in a ratio of 1:1) male and female

paediatric patients (age range from birth to <18 years) undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, planned for peripheral nerve block anaesthesiaand equally distributed within the two surgical procedures.

Inclusion criteria:

1. Male and femalepaediatric patients from birth to <18 years scheduled for:
   - 'calcaneo stop' surgery (6 to <18 years; children and adolescents)planned for sciatic nerve block short-lasting anaesthesia,
   - inguinal hernia repair (0 to 6 years; newborn infants, infants-toddlers and children)planned for ilioinguinal/iliohypogastric block short-lasting anaesthesia;
2. Normally active and otherwise judged to be in good health on the basis of medical history, physical examination, with normal lean body mass (BMI18,5 – 24,9 Kg/m^2 inclusive) and normal body development (normal weight and height according to local paediatric Height and Weight Chart);
3. ASA I and ASA II patients
4. Written informed consent provided by parents/tutor, willing and able to understand the purpose of the study, including possible risks and side effects, and willing and able to comply, on their behalf and of the minor, with the study requirements.
5. Willing and able to give additional written informed consent by itself, in case of children and adolescents, in addition to parents/tutor.
6. Willing and able, in case of children and adolescents, to comply with the study requirements on their behalf.

Exclusion criteria:

1. ASA > II patients
2. Preexistent infection at injection site;
3. Use of opioids, antidepressants, anticonvulsant, sulfonamide, vasopressors, ergot-type oxytocic drug and mixtures of local anaesthetics, antiarrhythmic drug class III, such as amiodarone, strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin;
4. Use of medication(s) known to interfere with the extent of regional blocks for 2 weeks before the start of the study;
5. History of drug or alcohol abuse;
6. Sensitivity among the study medication active ingredient, the members of the PABA esters group and amides-type local anesthetic group;
7. Clinical history of allergy, hypersensitivity or intolerance to the study medication or other medications used during surgery;
8. Pregnancy and lactation: positive pregnancy test at screening (if applicable), pregnant or lactating (the pregnancy test will be performed to all fertile subset)
9. Participation in any other clinical study within the 3 months prior to the screening.

Investigational medicinal product (IMP), dose and mode of administration:

Chloroprocaine HCl (benzoic acid, 4-amino-2-chloro-2-(diethylamino) ethyl ester, monohydrochloride) aqueous solutions for injection in two different concentrations, i.e.:

a) Chloroprocaine Hydrochloride 1%: (10 mg/mL); injectable solution, Sintetica S.A., Switzerland, 5 ml ampoules

b) Chloroprocaine Hydrochloride 2%: (20 mg/mL); injectable solution, Sintetica S.A., Switzerland, 20 ml vials

Duration of treatment:

1 day, a single, perineural, ultrasound-guided injection.

Pre-medication before surgery:

Patients will be pre-treated with:

- Midazolam: will be administered orally, only in patients > 6 months of age, 45 min before surgery,according to local routine practice.
- Sevoflurane by inhalation will be given, as recommended by local routine practice, in order to

induce general anaesthesia, after midazolam sedation and before IMP administration. Patients will breath unaided and, unless necessary as an emergency measure, they are not supposed to be intubated in the frame of this preoperative procedure.

Concomitant Medication after surgery:

- Paracetamol 15 mg/kg, will be injected i.v. immediately at the end of the surgery

Rescue anaesthesia during surgery:

Sensory block will be assessed by pin-prick test after chloroprocaine injection. In case of incomplete sensory block (when readiness for surgery not reached),fentanyl by IV injectionwill be given,at the dosage indicated by local routine practice, as rescue anaesthesia. All details about the administration of the rescue anesthesia will have to be recorded on the relevant CRF.

Permitted/Non permitted Concomitant Medications

Not allowed medications:

1. Vasopressors;
2. Ergot-type oxytocic ;
3. Sulphonamides;
4. Mixtures of local anaesthetics;
5. Opioids;
6. Antidepressants;
7. Anticonvulsants;
8. Antiarrhythmic drug class III, such as amiodarone;
9. Strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin.

Rescue medication:

Paracetamol, oral or suppository, at home (after home discharge)

Allowed medications:

Hormonal contraceptives for females of childbearing potential.

Treatment Compliance

Not applicable

Criteria for evaluation:

Primary efficacy endpoint:

The primary efficacy endpoint of the study will be represented by the overall proportion of patients, in each of the two dosage level groups, not requiring rescue anesthesia during surgery.

Secondary efficacy endpoints:

The secondary efficacy endpoints of the trial will be evaluated, unless otherwise specified, on the two dosage level groups separately and, in both the two dosage level groups, on the two surgical procedures. Secondary efficacy endpoints will be:

- Proportion of patients, in both of the two dosage level groups, not requiring rescue anaesthesia (fentanyl) during the two surgical procedures separately;
- Time to onset of sensory block, defined as the time period from completion of the injection (time 0 min) to the achievement of complete sensory block, assessed by pin-prick test associated with heart rate measurement, and evaluated for both surgeries;
- Time to regression of motor block evaluated in ‘calcaneo stop’ surgery only and assessed by a grade I of the standard Bromage scale (i.e. free movement of legs and feet). This evaluation will be performed immediately after the awakening and it will be repeated 30 minutes, 1 hour, 2 hours and 3 hours after the first evaluation, as well as

during the visit for discharge

- Pain intensity evaluated five times in the first 3 hours after patient's awakening and during the home discharge visit (V2). Post-surgery assessment will be performed immediately after the awakening and it will be repeated 30 minutes, 1 hour, 2 hours and 3 hours after the firstevaluation. The technique and appropriate scale for pain measurement are age-dependent therefore, different tools will have to be used for the evaluation:
  - COMFORT scale for patients <2 months of age;
  - FLACC scale for patients aged ≥ 2 months ≤ 6 years;
  - Wong-Baker scale for patients over 6 years of age;
- Time to eligibility for home discharge, defined as: "the time elapsed from completion of surgery to the time when criteria for discharge are met, regardless if the patient will be discharged from the hospital at a later time, according to the hospital procedures". The criteria for discharge will be defined according with the Pediatric Post Anesthesia Discharge Scoring System (Ped-PADSS)
- Time from completion of IMP injection to rescue anaesthesia, whenever required
- Posology of rescue anaesthesia, whenever required
- Proportion of patients requiring additional analgesia after surgery, other than paracetamol 15 mg/kg i.v. administered during the surgery as per hospital's standard procedures
- Type and posology of rescue analgesia required during the 7 days after surgery for each one of the two surgical procedures

Secondary safety endpoints:

The secondary safety endpoints of the trial will be evaluated on the two dosage level groups separately and, in both the two dosage level groups, on the two surgical procedures, and will be:

- Patient general recovery, evaluated by the Investigator through the evaluation questionnaire on the day of the intervention
- Patient general recovery, evaluated by the Investigator or his deputy through the F.U 24 H evaluation questionnaire on the day after intervention
- Patient general recovery, evaluated by the Investigator or his deputy through the F.U 7-day evaluation questionnaire 7 days after intervention
- Overall proportion and 95% CI of patients with prolonged post-operative temporary loss of sensation and/or motor activity
- Vital signs at rest (heart rate, systolic/diastolic blood pressure, respiratory rate, body temperature)
- Proportion of patients with AE, in each of the two dosage level groups and in the two surgical procedures
- Summaries of adverse events (AEs), including pain at injection site, neurological symptoms(such as: convulsion) and cardiac symptoms (such as bradycardia and heart failure etc.) evaluated, during surgery, after IMP injection

Statistical methods:

A fully detailed Statistical Analysis Plan will be prepared before the database lock.

Primary efficacy variable

Overall proportion of patients, in each of the two dosage level group, not requiring additional anaesthesia for the duration of the surgical procedure will be presented together with 95% CI.

Secondary efficacy variables

Given the exploratory nature of the study, statistical evaluations will be mainly descriptive.

Quantitative secondary endpoints will be summarized by means of descriptive statistics, as total number of evaluated subjects, mean, standard deviation, 95% confidence interval, median, minimum and maximum and number of missing values.

Categorical measures will be reported as frequency, percentages of observed values and 95% confidence interval.

Safety variables

Quantitative safety endpoints will be summarized by means of descriptive statistics as total number of evaluated subjects, mean, standard deviation, median, minimum and maximum and number of missing values.

Categorical safety endpoints will be reported as frequency and percentages of observed values.

Adverse Events and Serious Adverse Events (AEs/SAEs) will be represented by frequency and percentage of patients with AE/SAE; AEs/SAEs will be summarized by the MedDRA System Organ Class (SOC) and Low Level Term (LLT), when calculating the number of AEs/SAEs within each SOC and LLT, each subject will only be counted once.

Sample size estimate:

The size of this study is based on the A'Hern method for single stage phase II designs.We estimate as satisfactory a success rate of around 90% (p1=90%) or more, while a success rate of 80% (p0=80%) or less will be considered inadequate; following the A'Hern formula based on the exact binomial distribution and assuming an 80% power and alpha=0.05, the required sample size, for each group, is 82, with 72 being the minimum required number of successes to observe in order to reach a conclusion in favour of the treatment's efficacy.

Expected drop out rate for the primary endpoint is low given that a single dose injection is requested, and assuming a 5% drop out rate 87 patients in each study arm shall be enrolled. In total 174 patients will be enrolled.

Success rates and 95% CI will be presented separately for the two treatment groups, while a direct comparison will not be the focus of this study.

FPFV: September 2018

LPI: September 2020

LPO: October 2020

1.1 Study Flow Chart

Visits (Day)	V1/Screening (-3 Weeks to Day 0)	V2 (Day 1) Surgery/Discharge	FU phone call 1 (24 hrs)	FU phone call 2 (7 Days-1/+2 days)
Informed Consent Signature	**X**			
Medical History	**X**			
Physical Examination	**X**			
Demography (sex, weight, height, BMI)	**X**			
Vital signs(1) (blood pressure, heart rate)	**X**	**X**		
ECG(1)	**X** (2)	**X**		
Pregnancy test (3)	**X**	**X**		
Previous and Concomitant Treatments	**X**	**X**	**X**	**X**
Inclusion/Exclusion Criteria	**X**			
Enrolment	**X**			
Randomization		**X**		
Surgery		**X**		
IMPs administration		**X**		
Sensory block assessment (pin-prick test)(4)		**X**		
Motor block assessment (Standard Bromage scale (5)		**X**		
Post-surgery pain intensity by FLACC scale(6)		**X**		
Post-surgery pain intensity by Wong- Baker scale(7)		**X**		
Post-surgery pain intensity by COMFORT scale(11)		**X**		
Rescue medication during surgery		**X** (8)		

Patient/Caregiver diary dispensation		**X**		
Follow up questionnaire			**X**	**X**
Rescue medication end of surgery		**X**		
Rescue medication after home discharge			**X** (9)	**X** (9)
Home discharge		**X**		
Adverse Events(10)		**X**	**X**	**X**

1) Mandatory onlyfor infants aged 0-6 months at baseline visit, during the block until the end of the anaesthesia.
2) ECG at screening visit is discretionary and it will be performed in infants aged 0-6 months only if foreseen by the routine hospital procedures.
3) A urine pregnancy test will be performed only in fertile females. Kits will be provided by the Sponsor
4) Performed in case of Inguinal hernia repair and 'Calcaneo stop' surgery
5) Performed only in case of 'Calcaneo stop' surgery.
6) Only for patients aged from 0 to < 6 years.
7) Only for patients >6 years of age.
8) Fentanyladministration when readiness for surgery not reached.
9) Paracetamol intake after home discharge, recorded in parent's diary.
10) Severe neurotoxic or cardio-toxic events, caused by incorrect procedure leading to intravenous injection, will appear few minutes after Chloroprocaine administration and will be collected as SAE.
11) Only for patients <2 months of age

2. INTRODUCTION

2.1 Background information

2.1.1 Premise

The present protocol is part of an extensive Pediatric Investigational Plan (PIP) which has been submitted to the Paediatric Committee (PDCO) of the European Medicine Agency (EMA) in the contest of the marketing authorization application of chloroprocaine use for perineural block. Following a comprehensive examination of the overall plan and the adoption of some adjustments suggested throughout the discussion, the PDCO has adopted a positive opinion on both the PIP and the present clinical protocol.

2.1.2 Local anaesthesia and PNB

Regional analgesia, and specifically PNB, is an acceptable means of providing intraoperative anesthesia and postoperative analgesia in neonates, infants, and children while decreasing the use of systemic opioids and avoiding opioid-related adverse effects (1). With the advent of ultrasound and improvements in equipment in the last decade, the utilization of PNB in children has increased tremendously (2).
Moreover, regional anesthesia including PNB has been shown to have several potential beneficial effects in this population including earlier tracheal extubation, effective blunting of the surgical stress response, and limiting the need for parenteral opioids. The addition of regional anesthesia to general anesthesia can also be used to improve intraoperative conditions by providing muscle relaxation without the need for neuromuscular blockers (3).
The limitation of the requirements for volatile and other anesthetic agents may be desirable, given concerns regarding the potential impact of these agents on neurocognitive outcome in neonates and infants.
PNB should routinely perform in awake adults, because general anesthesia or heavy sedation removes all opportunity to communicate symptoms of potential nerve injury.On the other side, infants and children may be unable to communicate symptoms of potential peripheral nerve injury and uncontrolled movement may increase the risk of injury. Therefore, the placement of PNBs in children undergoing general anesthesia or heavy sedation may be appropriate (4).
For these reasons, actually, in contrast to adult practice, the majority of regional anaesthesia in children and infants is now performed under either deep sedation or general anaesthesia. Prospective and retrospective safety studies support the notion that performing regional anaesthesia under general anaesthesia is safe practice (5). Evidence-based literature shows that combined regional and general anaesthesia can decrease hospital stay and improve outcomes in paediatric patients (5).

2.1.3 Chloroprocaine

Chloroprocaine hydrochloride (Chloroprocaine HCl [benzoic acid, 4-amino-2-chloro-2-(diethylamino) ethyl ester, monohydrochloride]) is a short-acting local anaesthetic belonging to the amino-ester class, characterized by a rapid onset of action (usually 6 to 12 minutes) and anaesthesia duration up to 60 min, depending on the amount used and the route of administration. In-vitro chloroprocaine half-life is approximately 21-25 seconds.
In Switzerland (where the Applicant Sintetica S.A. is located), chloroprocaine hydrochloride has been authorized for epidural anesthesia and peripheral blocks since 1990 (Nesacaine® 1-2-3% injection, AstraZeneca). Of note, in 2007 the AstraZeneca reference drug product was withdrawn from the Swiss market. The action was undertaken for production technical reasons only, as reported by the Company, and

not for safety reasons. This is also stated in the Swissmedic Journal where withdrawal of the product was classified as a 'Marketing Authorization revocation following the decision of the company to forgo distribution' (Swissmedic Journal, July 2007).

Various formulations of preservative and antioxidant-free chloroprocaine HCl injectable solution for local anesthesia have been registered by the applicant in several countries. In particular, Sintetica S.A. is the Marketing Authorization Holder in Switzerland of chloroprocaine HCl 0.5% and 1% solutions for injection. This product, Ivracain® Sintetica (Chloroprocaine Hydrochloride 0.5%, Swissmedic registration n. 53,283), has been authorized and marketed since 1994 for intravenous regional anesthesia (IVRA) during upper and lower limbs surgery.

Sintetica S.A. is the Marketing Authorization Holder in Switzerland of chloroprocaine Hydrochloride (HCl) 0.5% and 1% solutions for injection. This product, Ivracain Sintetica (Chloroprocaine Hydrochloride 0.5%), has been authorized and marketed since 1994 for intravenous regional anesthesia (IVRA) during upper and lower limbs surgery.

Chloroprocaine Hydrochloride 1% Sintetica has been on the Swiss market since 2002 for local anesthesia and PNBs. This formulation was locally distributed according to Swiss law "Formula Hospitalis" beginning in 2002 and was subsequently registered as medicinal product in 2008. Chloroprocaine Hydrochloride 1% Sintetica has also been imported by various hospitals in Belgium.

In Europe, on March 19, 2012, following decentralized procedure, Marketing Authorization was obtained from the German Authority for Sintetica's Chloroprocaine hydrochloride (Ampres) 1% for intrathecal administration. The product was assigned the status of New Active Substance. This marketing authorization was based on published literature plus non-clinical and clinical trials sponsored by the applicant Sintetica S.A.

Currently, Chloroprocaine HCl 1% for intrathecal administration (under the brand names of Ampres/Clorotekal/Decelex) is registered in 9 European countries (Germany, Austria, France, Belgium, Spain, UK, Ireland, Poland and Italy). Via the registration process in Europe, Ampres 1% is currently licensed for intrathecal (spinal) anesthesia in adults where the planned surgical procedure is not expected to exceed 40 minutes.

In July 2015, the applicant obtained Marketing Authorization approval in Switzerland for chloroprocaine HCl 10 mg/mL, 20 mg/mL and 30 mg/mL solutions for injection, for local anesthesia by infiltration, for PNB and epidural block, respectively, under the brand name Ampres 1, 2 and 3%.

Whereas Chloroprocaine HCl 2% solutions are presently on the market in USA, Canada and Switzerland for the production of local anaesthesia by PNB and other administration routes, in Europe this local anaesthetic is not presently marketed as a 2% solution for the PNB indication, neither in adults nor in pediatrics.

2.1.4 Safety of local anaesthetics

The mechanism of action of 2-chloroprocaine is the same of LAs that produce reversible loss of sensation, when applied to nervous tissue. Their primary site of action is the cell membrane and they produce their effect interacting directly with voltage-gated Na+ channels. It is now generally accepted that the mechanism of action of these compounds is based on the interaction with specific binding sites within the Na+ channels resulting in a blockade of the Na+ current. In higher concentrations, the other ion channels (K+, Ca++) might be affected as well (6).

The most important clinical properties of LA agents are potency, onset, duration of action and blockade of sensory and motor fibres. These qualities are primarily dependent by physico-chemical properties of the compounds. The chemical structure of LA agents consists in 3 parts that affect the PK and pharmacodynamic properties: a lipophilic part, a hydrophilic part, and a chain that links the two parts.

LAs can be divided in two groups according to the chemical link between lipophilic and hydrophilic parts: amide type drugs metabolized by hepatic microsomal enzymes, and ester type drugs, like 2-chloroprocaine, hydrolyzed readily by plasma esterases. The potency and the duration of action of the anesthetics depend mainly on lipid solubility protein-binding and pKa (7).

Local anesthetic toxicity is extremely rare in infants and children; specifically, if appropriately administered, in terms of dosage and anatomical location, PNB are relatively free of adverse effects. Relative contraindications include local infection, generalized sepsis, coagulopathy. Local anaesthetic systemic toxicity (LAST) ranges from mild systemic symptoms (auditory changes, circumoral numbness, metallic taste and agitation), to central nervous system findings (seizure, coma, respiratory arrest) and cardiovascular events (hypertension, hypotension, tachycardia, bradycardia, ventricular arrhythmias, cardiac arrest) (8). Peripheral nerve injury is an infrequent complication of regional anaesthesia. Because neurological injuries after PNBs are so rare, it is extremely difficult to obtain reliable and consistent data about their incidence. Most injuries are transient and often subclinical, or present as mild mononeuropathies. Allergic reactions with local anaesthetics are rare but could occur in patients hypersensitive to ester groups and could consist of pruritus, urticaria, edema and tachycardia. Central nervous system and cardiovascular system adverse reactions are generally dose-related and occur only with high plasma concentrations of local anaesthetics. These reactions are not expected with the indication of the present clinical protocol.

2.1.5 Chloroprocaine use in pediatric population

To date there are limited data regarding the use of chloroprocaine in the pediatric patient. Interest in the use of 2-chloroprocaine for regional anesthesia in infants began in the early 1990s. At this time, regional anesthesia alternatives to general anesthesia were being sought to avoid postoperative apnea in preterm infants. The most common use of spinal anesthesia in the pediatric population is for preterm infant at risk for postoperative apnoea following general anesthesia. Spinal anesthesia is easiest to perform in infants weighing less than 3 kg, and is most practical when the duration of the surgical procedure is less than 90 minutes.

Although spinal anesthesia and single shot caudal epidural anesthesia were effective, the duration of surgical anesthesia with such techniques was limited, thereby eliminating the potential for more prolonged surgical procedures.

Because of its extremely short duration of action, chloroprocaine has been used primarily for continuous epidural techniques in infants and children (3; 9; 10) and for femoral and lateral cutaneous nerve block in older children having muscle biopsy (11). Measured blood chloroprocaine concentrations in a very limited number of infants have been either zero or extremely low (9). None of the patients required supplemental analgesia, none required conversion to general anesthesia, and there were no reported complications.

In adolescent, spinal anesthesia may be offered as an alternative to general anesthesia for low abdominal and lower-extremity procedures.

Continuous caudal epidural infusion of 3% 2-chloroprocaine was utilized as an adjunct to general anesthesia (3; 12) limiting intraoperative opioid and volatile agent requirements allowing for earlier postoperative tracheal extubation.

There are no reports of either sustained neurologic deficits or back pain after the use of chloroprocaine in pediatrics; however, most patients are infants or children with no, or limited, ability to communicate (13).

2.1.6 Ultrasound-guided PNB in children

Several clinical studies show that PNBs can be performed in neonates and children to provide analgesia for several different surgeries (14; 15; 16; 17; 18; 19). Lidocaine, mepivacaine, bupivacaine, ropivacaine and, more recently, levobupivacaine are used worldwide for peripheral nerve blocks (20), as well as chloroprocaine (in US, Canada and Switzerland). Recently, the advancement in ultrasound technology has facilitated the placement of nerve blocks in children of all ages. Importantly, dosing has been decreased to a great extent, and accurate localization has provided more efficacious blocks. In addition, vascular structures are avoided. The main advantages conferred by ultrasonographically-guided techniques in children are the imaging of all anatomical structures and the possibility of directly ascertaining the position of the tip of the cannula relative to the nerve (21). Consequently, damage to important structures like nerves and vessels, during the injections, can be avoided and the risk of accidental nerve damage can be reduced, although care should be continually exercised using standard safety precautions to minimize any possible risk associated with the technique. Additional advantages lie with the faster onset of sensory and motor blocks, longer duration of blocks and increased block quality and success rate (22). In children, ultrasound-guided block dramatically reduces the volume of local anaesthetic required.The use of new technologies, such as ultrasound-guided regional anesthesia, that has shown several advantages in both the efficacy and safety profile of LAs, combined to the use of chloroprocaine, nowadays the safest LA, may represent the best choice in regional anesthesia in pediatrics.

2.2 Study rationale

In children, nerve fibres are thinner, they have less myelin and the nodes of Ranvier stay closer to each other. Consequently, a regional block in children may spread further than the provider intends. Additionally, because the local anesthetic spreads easily in children, the duration of the block may be shortened compared to an adult. In general, as the patient's age increases, local anesthetic latency of onset and duration of action increases as well.

The LA should be tailored to the duration of the surgical procedure and the anticipated degree of pain. Therefore, selection of a short-acting agent such as chloroprocaine provides excellent intraoperative conditions, without the burden of an insensate limb for 10 to 18 hours postoperatively. For a greater degree of postoperative pain, the selection of a long-acting LA (e.g., ropivacaine) is more appropriate.

Onset and duration for a given LA varies according to the nerve or plexus blocked. For example, at the brachial plexus, 0.5% ropivacaine may be expected to provide 10 to 12 hours of analgesia; the same concentration at the sciatic nerve may provide up to 24 hours of analgesia. This is likely due to differences in the local vascularity, which influences the uptake of LA.

Of note, blocks for postoperative analgesia (often in concert with general anesthesia) do not require a high concentration of LA. Pediatric ambulatory patients who are undergoing short procedures with minimal postoperative pain (most ambulatory procedures) only require a short- to intermediate-acting agent. Short acting local anesthetic agents such as chloroprocaine may result the anesthetic of choice given its rapid onset, good intra-surgery control, very low toxicity profile, fast recovery offering the advantage of early home discharge.

Calcaneo stop and inguinal hernia repair have been proposed as model surgeries to assess chloroprocaine efficacy and safety in pediatric patients in consideration that:

- They are two types of ambulatory surgeries very commonly performed in pediatric hospitals.
- They are highly representative for the clinical practice followed in European sites.
- The proposed surgeries are highly reproducible from a procedural point of view among different centres.
- They are considered ideal surgeries to test the efficacy properties of an anesthetic such as chloroprocaine. Indeed, they are both minor outpatient surgeries, where a very rapid onset of sensor and motor block is desirable to allow the management of pain limited to intra-operatory period. The management of post operatory pain can be achieved by the use of mild analgesics such as paracetamol and ibuprofen.
- They are two outpatient surgeries that do not require the burden of sensor and motor block for several hours postoperatively.

Importantly, short procedures with minimal postoperative pain (ambulatory procedures such as calcaneo stop and inguinal hernia repair) that only require a short- to intermediate-acting agent are considered the ideal surgeries for testing the clinical efficacy and safety of short acting local anesthetic agents such as chloroprocaine.
The proposed operations may thus faithfully represent two of the more diffused medical conditions that need to be treated by mean of outpatient surgeries in the pediatric population; these two ambulatory surgeries can therefore considered representative to the product's future clinical use of the product. Moreover, the inclusion of both the surgeries in the planned pediatric study permits a coverage of all the pediatric subsets (from preterm/neonates to adolescents).

2.3 Risks and benefits

2.3.1 Risks

Potential risks of PNBinclude vascular puncture and bleeding, nerve damage and local anesthetic sistemic toxicity (LAST). Despite these potential dangers, clinical evidence shows that PNB procedures are very well tolerated if appropriately administered in terms of dosage and anatomical location.

2.3.2 Benefits

Clinical evidence demonstrates the benefits of PNB in terms of clinical outcomes. In particular, the adoption of PNB techniques has been associated with improvements in postoperative pain control and reduction in the use of opioids(which in turn minimizes the risk of adverse events), Thanks to the recent advances in ultrasound technology,an optimal needle placement can be achieved with very low dosage of anesthestic, which makes PNB an optimal option for children.

Given the abovementioned considerations,as well as the ascertained safety of chloroprocaine, the risk-benefit profile for the conduct of this study appears to be favorable, thus making the investigational product an optimal candidate to be tested as a PNB agent in pediatric population undergoing ambulatory, short-term surgeries.

According to clinical experience, recruitment rate of the study could be very critical due to the lower incidence of day-case short duration surgical procedures in pediatric population as compared to adults. For this reason a six months rate check will be performed. In case recruitment rate is found to be lower than

expected (i.e. two patients/month), a protocol amendment will be submitted to include additional clinical centres in the study and to ask for a further delay of the study.

3. STUDY OBJECTIVES

The general objective of the study is to evaluate, in pediatric population undergoing 'calcaneo stop' surgery or inguinal hernia repair, the efficacy and safety of chloroprocaine 1% and 2% for peripheral nerve block based on concentration–response relationships.

3.1 Primary Objective

The primary objective of the study is the assessment of the efficacy of perineural injection of chloroprocaine 1% and 2% in pediatric population for a successful peripheral nerve block (same volume ml/Kg) in terms of proportions of subjects not requiring rescue anesthesia during surgery.
In the context of the present clinical protocol, a peripheral nerve block is defined as successful if the induced anaesthesia is adequate for the surgery (complete sensory block) without any supplementation in the first 45 min (even if surgery lasts for > 45 min), calculated from the time of readiness for surgery (complete sensory block).

3.2 Secondary Objectives

Efficacy:

The secondary, efficacy objectives of the trial will be evaluated on the two dosage level groups separately, on the two surgical procedures, considering both dosage levels, and will consist in the assessment of the following parameters:

- time to onset of sensory block starting from completion of the IMPs injection (corresponding to readiness for surgery), detected by pin-prick testin case of Inguinal hernia repair (ileogastric/ileoinguinal nerve block).The response to pinprick in sedated patient will be associated to at least a 20% increase from baseline in heart rate (HR). The sensory block onset will be achieved if no apparent hemodynamic reaction to pinprick will be seen (defined as an increase in heart rate in excess of 20% compared with baseline levels), meaning that the patient is ready for surgery.
- time to onset of sensory block starting from completion of the IMPs injection (corresponding to readiness for surgery), detected by pin-prick test in case of ‘calcaneo stop’ (sciatic nerve block). The measurement of the heart rate will serve as confirmatory test as for inguinal hernia repair surgery.
- time to regression of motor block (sciatic nerve block) by standard Bromage scale, at the start of patient’s awakening,in case of calcaneo stop procedure. The assessment will be repeated 30 minutes, 1 hour, 2 hours and 3 hours after the first evaluation This phase will have to be monitored with particular care since events of agitation followed by numbness are very common in children after sevoflurane anesthesia.
- pain intensity, assessed five times in the first 3 hours after the end of surgery and during the home discharge visit (V2). Post-surgery assessment will be performed immediately at awakening and 30 minutes, 1 hour, 2 hours and 3 hours after this first evaluation. The following tools will be used for pain evaluation: COMFORT scale for patients <2 months of age, FLACC scale for patients aged ≥ 2 months ≤ 6 years, and Wong-Baker scale for patients over 6 years of age, respectively;

- time to eligibility for home discharge defined as: "the time elapsed from completion of surgery to the time when criteria for discharge are met, regardless if the patient will be discharged from the hospital at a later time, according to the hospital procedures". The criteria for discharge will be defined according with the Pediatric Post Anesthesia Discharge Scoring System (Ped-PADSS).
- if rescue anaesthesia (fentanyl) was required during both surgical procedures performed;
- time and dosage of rescue anaesthesia (fentanyl) required during surgery, in addition to Investigational Medicinal Products (IMPs) injection;

Safety:

The secondary, safety objectives of the trial will be to assess:

- the general tolerability and safety of the study drug, assessed through summaries of adverse events;

- Pain at injection site, neurological symptoms (such as: convulsions) and cardiac symptoms (such as bradycardia and heart failure etc.) evaluated during surgery after IMP injection.

4. STUDY DESIGN

4.1 Study overview and plan

This is a prospective, randomized, multicenter, double blind, parallel active groups, concentration-response model, phase II clinical trial, aimed at evaluating the efficacy and safety of chloroprocaine 1% and 2% for peripheral nerve block in pediatric population undergoing 'calcaneo stop' surgery or inguinal hernia repair, based on concentration–response relationships. 'Calcaneo stop' and inguinal hernia repair have been chosen as testing surgeries based on the following considerations:

- Calcaneo stop surgery is a common, simple, reliable, and minimally invasive procedure for the treatment of pediatric flexible flatfoot performed on children from 6 years to adolescence. Sciatic nerve block offers minimal postoperative pain control after calcaneo stop surgery in children (23) and effective analgesia is achieved by use of paracetamol. Flexible flatfoot is the most prevalent condition seen in pediatric orthopaedic clinics; according to the published data, the incidence is about 5% in children and adults (24). The mean surgery duration is about 15-30 minutes.

- Inguinal hernia repair is globally the most frequently performed surgical procedures in children (25). At the end of operation, most children only need paracetamol or ibuprofen by mouth every four to six hours for the first 24 hours after surgery. The overall incidence of inguinal hernias in childhood ranges from 0.8% to 4.4%. One third of all children with hernias present before six months of age and outpatient surgeries may be routinely performed on children till 6 years of age. The incidence is much higher in premature infants; inguinal hernias develop in 13% of infants born before 32 weeks gestation and in 30% of infants weighing less than 1000 g (25). Importantly, many surgeons repair inguinal hernias before discharge from the neonatal intensive care until once the infants reach 1800 to 2000g (26), with babies that on some occasions are less than 2 months. The mean surgery duration is about 30-45 minutes.

The study consists of a treatment period of 1 day and of a single perineural injection, administered through ultrasound-guided technique in order to avoid the risk of chloroprocaine IV injection.

The Principal Investigator's site will be located Italy, the other involved study sites are indicatedin the Site List provided separately from the present document.The number of patients to be included is 174 (87 per treatment group, allocated to 1% or 2% arm in a ratio of 1:1 according to the randomization list). Details about the randomization procedure are reported in section 6.

Two IMPs will be used during the trial, namely Chloroprocaine Hydrochloride (benzoic acid, 4-amino-2-chloro-2-(diethylamino) ethyl ester, monohydrochloride) aqueous solutions for injection,at a concentration of 1% and 2%, respectively

IMPs will be injected after induction of general anaesthesia; onset of sensory block induced by Chloroprocaine HClwill be assessed by pin-prick test associated with heart rate assessment (for both sciatic nerve or ilioinguinal/iliohypogastric nerve blocks) before surgery.

The treatment periodlasts for 1 day and consists of a single, perineural, ultrasound-guided injection.

Before surgery, patients will be administered a pre-IMP treatment according to the following pattern:

- Midazolam,that will be administered orally, only in patients > 6 months of age, 45 min before surgery (according to local routine practice); and
- Sevofluraneby inhalation will be given, as recommended by local routine practice, in order to induce general anaesthesia, after midazolam sedation and before IMP administration. Patients will breath unaided and, unless necessary as an emergency measure, they are not supposed to be intubated in the frame of this preoperative procedure.

Immediately after the end of the surgical intervention, all patients will be administered Paracetamol 15 mg/kg, byi.v. injection

The study consists of 2 visits, and 2 telephone follow-up calls, in accordance with the following schedule:

- Screening visit (V1);
- Surgery and discharge visit (V2);
- Follow Up safety phone call Day 1(24 hours post-surgery);
- Follow Up safety phone call Day 7 (7 Days-1/+2 days post-surgery).

5. STUDY POPULATION

5.1 Number of Patients

The number of patients to be recruited is estimated to 174 patients undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, and fulfilling the eligible criteria indicated below. Further details are reported in section 11.1 (Rationale for sample size calculation).

5.2 Inclusion Criteria

1. Male and female paediatric patients from birth to <18 years scheduled for one of the following surgical procedures whose duration, according to clinical experience, should not exceed 45 minutes:
   - 'calcaneo stop' surgery (6 to <18 years; children and adolescents) planned for sciatic nerve block short-lasting anaesthesia,

- inguinal hernia repair (0 to 6 years; newborn infants, infants-toddlers and children) planned for ilioinguinal/iliohypogastric block short-lasting anaesthesia;

2. Normally active and otherwise judged to be in good health on the basis of medical history, physical examination, with normal body mass index (BMI18,5 – 24,9 Kg/m^2 inclusive) and normal body development (normal weight and height according to local paediatric Height and Weight Chart);
3. ASA I and ASA II patients
4. Written informed consent provided by parents/tutor, willing and able to understand the purpose of the study, including possible risks and side effects, and willing and able to comply, on their behalf and of the minor, with the study requirements.
5. Willing and able to give additional written informed consent by itself, in case of children and adolescents, in addition to parents/tutor.
6. Willing and able, in case of children and adolescents, to comply with the study requirements on their behalf.

5.3 Exclusion Criteria

1. ASA > II patients
2. Preexistent infection at injection site;
3. Use of opioids, antidepressants, anticonvulsant, sulfonamide, vasopressors, ergot-type oxytocic drug and mixtures of local anaesthetics, antiarrhythmic drug class III, such as amiodarone, strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin;
4. Use of medication(s) known to interfere with the extent of regional blocks for 2 weeks before the start of the study;
5. History of drug or alcohol abuse;
6. Sensitivity among the study medication active ingredient, the members of the PABA esters group and amides-type local anesthetic group;
7. Clinical history of allergy, hypersensitivity or intolerance to the study medication or other medications used during surgery;
8. Pregnancy and lactation: positive pregnancy test at screening (if applicable), pregnant or lactating (The pregnancy test will be performed to all fertile subset)
9. Participation in any other clinical study within the 3 months prior to the screening.

6.CRITERIA AND PROCEDURE FOR RANDOMIZATION

6.1 Treatment allocation

The study treatment will be administered to all the participants at Visit 2, before surgical intervention. All eligible patients will be allocated to the relevant treatment group through a randomization list which will be prepared in accordance with the following criteria:

- The full study population (n = 174) will be equally distributed between the two treatment arms (87 patients for chloroprocaine 1% and 87 patients for chloroprocaine 2%);

- Within each treatment arm, 43 patients will undergo inguinal hernia repair surgery and 44 patients will undergo calcaneo stop surgery;

- In order to ensure adequate representation of all age ranges, the minimum number of participants in each of the age subsets is expected as follows:

    a. Preterm and/or term newborn infants (0-27 days) n = 26
    b. Infants and toddlers (28 days to 23 months) n = 30
    c. Children 2-6 (2 to 6 years) n = 30
    d. Children 6-11 (6 to 11 years) n = 44
    e. Adolescents (12 to 18 years) n= 44

6.2 Blinding

The present study will be conducted according to a Double-Blind model: none of the involved players (patient, caregiver, investigator, outcomes assessor) will thus be aware of the treatment allocation.Once eligibility is established, the treatment assignement will be performed via web, by means of an allocation system embedded in the e-CRF platform. All details about the procedure to be followed for the treatment assignment will be provided in the IMP Manual which will be supplied to the investigators prior to site activation.
The original randomization list will be developed and kept by the designated CRO as well as by the Sponsor.
Syringes for injection will be prepared in an area adjacent to the operating room by a person not involved in any other study activity. Right after preparation, the syringe will be given to the blinded anesthetist who will proceed with the administration by means of a line which will have to be long enough to keep the syringe out of the sterile area. The operator in charge of the study drug preparation will take care of completing the IMP sheet that will be present in each package.The completed sheet will be kept together with the other patient records under responsibility of the investigator.

6.3 Emergency unblinding

The blinding of the trial will be maintained for the entire duration of the study until database lock, however, participants may be unblinded during the trial for the occurrence of a medical emergency. To this aim, each IMP kit will be supplied together with the relevant sealed envelope to be used for code break in case of emergency. The envelopes will be brown-colored and will not have any window, in order to ensure that the contents cannot be seen when held up to the light. A detailed Standard Operating Procedure (SOP) to be followed to perform the code break will be provided to the investigators. If unblinding is required, the following information will have to be recorded by the involved site staff (Principal Investigator, Co-investigator, Pharmacist):

- Date and time of the code break
- Reason for the unblinding
- Actions taken
- Details of the person(s) involved in the code break
- Patient study number/trial identifier

All code break envelopes must be collected by the PI and reconciled by the clinical monitor at the end of the study

7.STUDY CONDUCT

7.1 Study Duration

The study protocol foresees a screening visit (that could be performed from three weeks before the surgery), 1 study treatment for each patient, followed by 2 telephone follow up calls (24 hours and 7 days after surgery).
Themaximum study duration will be approximately 28 days, screening visit and follow-up included.A detailed list of the study assessments and related timeframes is reported in sections 7.2 (Detailed study plan) and 1.1 (Study Fow Chart).

7.2 Detailed StudyPlan

7.2.1 VISIT V1: Screening phase

During the screening phase, fulfilment of eligibility criteria will be verified.The following tests and procedures will be performed:

1. Informed Consent review and signature;
2. Inclusion and exclusion criteria assessment;
3. Medical history;
4. Demography (sex, weight, height, BMI);
5. Vital signs (blood pressure, heart rate);
6. ECG (when relevant);
7. Previous and concomitant treatments;
8. Pregnancy test (when relevant);
9. Enrolment;

7.2.2 VISIT V2: Surgery and Discharge (Day1)

The screened patients will be considered eligible for randomizationonce the following conditions will be fulfilled:

a. all procedures, tests and examination required during the screening visits have beencompleted; and
b. all eligibility criteria for entry into study are met

The following tests and procedures will be performed:

1. Vital Signs (blood pressure and heart rate);
2. ECG (when relevant);
3. Pregnancy test (when relevant);
4. Previous and concomitant treatments;
5. Randomization;
6. IMPs administration;
7. Surgery
8. Sensory block assessment (pin-prick test, before intervention, for both surgeries);

9. Motor block assessment (Standard Bromage scale, after patient's awakening, for 'calcaneo stop' surgery only);
10. Assessment of post-surgery pain intensity by one of the following scales according to patient's age:
    a. FLACC scale (for patients aged ≥ 2 months ≤ 6 years)
    b. Wong-Baker scale (for patients over 6 years of age)
    c. COMFORT scale (for patients <2 months of age);
11. Rescue medication during surgery;
12. Parent/Caregiver diary dispensation;
13. Rescue medication end of surgery;
14. Evaluation of eligibility for home discharge (Ped-PADSS);
15. Recording of Adverse events;

7.2.3 TELEPHONE FOLLOW UP VISITS

FU Day 1 (24 hrs post-surgery)

The following tests and procedures will be performed:

1. Recording of concomitant treatments;
2. Follow up questionnaire;
3. Recording of rescue medication after home discharge;
4. Recording of Adverse Events;

FU Day 7 (-1/+2 days post-surgery)
The test and procedures described below will be performed:

1. Recording of concomitant treatments;
2. Follow up questionnaire
3. Recording of rescue medication after home discharge;
4. Recording of Adverse Events.

8.TRIAL PROCEDURES AND ASSESSMENTS

8.1 Physical examination and vital signs

A comprehensive physical examination inclusive of vital signs measurements at rest (height, weight, temperature, blood pressure, heart rate, respiratory rate and BMI) will be performed at the screening visit. Vital signs will be performed at baseline, during the block until the end of the anaesthesia.

- Height: in children younger than two years, body length should be masured in the supine position. In older children, the height measurement should always be done with the patient standing.

- Weight: it is recommended to use a scale with the following features:
    - Solidly built and durable
    - Electronic (digital reading)
    - Measures up to 150 kg
    - Measures to a precision of 0.1 kg (100g)
    - Allows tared weighing

Children younger than two years may be weighed through tared weighing while held by the parent or tutor. Whenever possible, it is recommended to weigh older children alone, in standing position.It is recommended to remove clothing before weighing, in order to obtain a more accurate measurement.

- Temperature: rectal temperature recordings are preferred in infants and children younger than two years, axillary recordings are recommended for older patients. According to the local routine, both digital and mercury-glass thermometers can be used for the recording.

- Blood Pressure: devices for the measurement of blood pressure may include the standard extremity cuff and mercury bulb sphygmomanometer, the hand-held aneroid manometer, and the doppler and oscillometric devices. Any of the abovementioned procedures can be acceptable in the frame of this study as long as the blood pressure is measured according to the local routine procedure. Regardless the adopted procedure, it is suggested that patients old enough to understand should be shown the blood pressure device before the examiner attempts to take a measurement. The patient should be allowed to play with the device or feel the cuff inflate to gain his or her cooperation.

- Heart rate: The heart rate can be measured by direct auscultation or palpation of the heart or peripheral arteries (carotids, femorals, brachials, or radials).

- Respiratory rate: The respiratory rate can be obtained by auscultation, palpation, or direct observation

- BMI: Body Mass Index should be determined according to the following formula:

  Weight in kg ÷ squared length/height in metres

  It is very important to use a length measurement for a child less than 2 years old and a height measurement for a child age 2 years or older. If necessary, convert height to length (by adding 0.7 cm) or length to height (by subtracting 0.7 cm) before determining the child's BMI.
  A BMI Table and related reading procedure will be provided to the study investigators prior to study initiation.

8.2 Electrocardiogram

An ECG,foreseen only for infants aged 0-6 months, will be performed at screening (only if foreseen by the routine hospital procedures) and baseline visits, respectively.
The electrodes will have to be placed in theirusual positions, and any effort should be done in order to prevent the child from moving during the acquisition.

8.3 Sensory block assessment

Sensory block is defined as absent thermal and sensitive perception in each nerve territory. In this study, sensory block will be evaluated using the pin-prick test technique. The stimulation will be done every 4 to 5 minutes after IMP injection,by means of pliers on the area of intervention, with the patient asleep, right before the start of the surgery. The response to pinprick in sedated patient will be associated to at least a 20% increase from baseline in heart rate (HR). The sensory block onset will be achieved if no apparent hemodynamic reaction to pinprick will be seen (defined as an increase in heart rate in excess of 20%

compared with baseline levels), meaning that the patient is ready for surgery.Once the sensory block has been achieved the investigator will start the surgery according to local routine practice.

8.4 Motor block assessment

The time to regression of motor block, foreseen only for 'calcaneo stop' surgery, will be assessed by means of the standard Bromage scale (27). The evaluation will be performedimmediately at patient's awakening and it will be repeated 30 minutes, 1 hour, 2 hours and 3 hours after the first evaluation. The awakening phase will have to be monitored with particular care since events of agitation followed by numbness are very common in children after sevoflurane anesthesia.
In the standard Bromage scale, the intensity of motor block is assessed by the patient's ability to move his/her lower extremities. When using this scale for research in labour analgesia, it is important to measure motor block intermittently throughout labour, as the degree of block will change. It is also important to measure motor block in both legs, since the block may be asymmetrical. Although several modifications of the Bromage scale have been described, including the use of more gradations of motor block, in the present study we refer to the standard one, whose levels of measurement are described by the table below:

Grade	Criteria	Degree of block
I	Free movement of legs and feet	Nil (0%)
II	Just able to flex knees with free movement of feet	Partial (33%)
III	Unable to flex knees, but with free movement of feet	Almost complete (66%)
IV	Unable to move legs or feet	Complete (100%)

8.5 Post-surgery pain intensity

Pain intensity will be evaluated for both surgeries at different timepoints: five times in the first 3 hours after patient's awakening and during the home discharge visit (V2). Post-surgery assessment will be performed immediately after the awakening and it will be repeated 30 minutes, 1 hour, 2 hours and 3 hours after the first evaluation. The technique and appropriate scale for pain measurement are age-dependent therefore, different tools will have to be used for the evaluation:

8.5.1 COMFORT scale for patients aged < 2 months of age

The COMFORT Scale (28) is a pain scale that may be used to assess pain when a person cannot describe or rate their pain. For this reason, some of the common populations this scale might be used with include:

- children
- cognitively impaired adults
- adults whose cognition is temporarily impaired, by medication or illness
- the learning disabled
- sedated patients in an ICU or operating room setting

The COMFORT Scale is based on the evaluation of 9 parameters (alertness, calmness, respiratory response, crying, movement, mean arterial blood pressure, heart rate, muscle tone and facial expression), all ranging between 1 and 5 (maximum distress indicated by 5 points). Overall, it provides a pain rating between 9 and 45.

8.5.2 FLACC scale for patients aged ≥ 2 months ≤ 6 years

The FLACC (29) is a behavioral scale that has been validated for assessment of postoperative pain in children between the ages of two months and seven years. The acronym "FLACC" represents five categories: face, legs, activity, cry and consolability. Responses in each category are scored between 0 and 2, foa a maximum total score of ten. To use the FLACC scale the clinician should observe a child for one to five minutes. A pain score is obtained by reviewing the descriptions of bahavior in each of the FLACC categories and selecting the number that most closely matches the observed behavior. The numbers obtained for each category are added together to obtain the total pain score, which will be between 0 and 10. It may be necessary to touch and reposition the child to determine if pain is present with movement and to better assess tension and rigidity in the body.

8.5.3 Wong-Baker scale for patients over 6 years of age

The Wong Baker Faces Pain Scale (30) combines pictures and numbers to allow pain to be rated by the user. It can be used in children over the age of 3, and in adults. The faces range from a smiling face to a sad, crying face while the numerical rating assigned to each face is arranged in six levels, 0-2-4-6-8 and 10 respectively, with the 'zero' (smiling face) corresponding to the absence of pain and the '10' (crying face) corresponding to an extreme hurt.

8.5.4 Pediatric Post Anesthesia Discharge Scoring System (Ped-PADSS)

The Ped-PADSS (31, 32) is a a pediatric adaptation of the postanesthetic discharge scoring system (PADSS), a gold standard to assess home readiness after ambulatory surgery in adults (33, 34). Ped-PADSS was built using validated criteria extracted from Chung's PADSS. The five items - hemodynamic status, level of consciousness, pain, nausea and vomiting, and bleeding of the surgical site - are recorded on a scale from 0 to 2. A Ped-PADSS score ≥9 at 1-h intervals is needed to allow discharge from the hospital with the following three additional conditions required: absence of any breathing difficulty or hoarse voice; no request from parents to see the anesthetist before discharge; no requirement wish of the anesthetist to see parents or child before discharge.

8.6 Post-discharge assessments

The post-operative progress, mainly as to what concerns patients' safety and well-being,will be monitored until 7 days after discharge. In particular, the following information will be collected: pain at the injection site, pain at the site of surgery, occurance of expected/unexpected adverse events, concomitant medications. Post-operative progress after discharge will be monitored by means of the following tools:

a) the Investigator or his deputy will contact the patients by telephone and will question them about any adverse reactions which might have occurred after discharge. Neurological and other symptoms will be assessed through an interview using a specific questionnaire, that will be performed twice (24 hours and 7 days after surgery, respectively)
b) weekly diary, to be completed (by the patient or caregiver depending on participant's age) every day during the first week after discharge. A copy of the completed diary will have to be returned to the site via email, fax or courier, as agreed with the investigator at the time of diary dispensation.

A sample copy of both the questionnaire and the diary is provided in Appendixes 17.5 and 17.6, respectively.

9.STUDY DRUG

9.1 Study Drugs Description

Two IMPs will be used during the clinical study - Chloroprocaine HCl (benzoic acid, 4-amino-2-chloro-2-(diethylamino) ethyl ester, monohydrochloride) aqueous solutions for injection in two different concentrations, i.e.:

- Chloroprocaine Hydrochloride 1%: (10 mg/mL); injectable solution, Sintetica S.A., Switzerland, 5 ml ampoules
- Chloroprocaine Hydrochloride 2%: (20 mg/mL); injectable solution, Sintetica S.A., Switzerland, 20 ml vials

IMPs shelf-life: Chloroprocaine HCl1% and 2% are commercially available and authorized with a shelf-life of 30 months and 36 months respectively.

IMPs storage conditions: Chloroprocaine HCl1% and 2% must be stored protected from light, in sealed original packaging and at room temperature (15-25° C).

Further details about study drug preparation and handling are reported in the IMP Manual provided to the investigators.

9.2 Dosage and administration

Doses to be used during the study:

- Sciatic nerve block for 'Calcaneo stop' surgery: 0,5 ml/kg for both IMPs (Chloroprocaine HCl1% and Chloroprocaine HCl2%);
- Ilioinguinal/iliohypogastric nerve block for inguinal hernia repair: 0,3 ml/kg for both IMPs (Chloroprocaine HCl1% and Chloroprocaine HCl2%).

IMPs will be injected after induction of general anaesthesia; onset of sensory block induced by Chloroprocaine HCl will be assessed by pin-prick test for both sciatic nerve or ilioinguinal/iliohypogastric blocks.

- The investigational medicinal products will be administered by ultrasound-guided perineural injection,to be performed very slowly, with repeated aspirations, with the patient asleep for the effects of the general anesthesia and positioned supine. The needle (whose length will be calibrated on the basis of the type of surgery as well as of other relevant parameters such as patient's age and anthropometric measurements) will be inserted via a lateral approach, in-plane with the transducer and perpendicular to the ultrasound beam in order to optimize needle visualization. The ultrasound transducer will work at high frequency.

Site of Injection: Sciatic nerve (mid-thigh region) for 'Calcaneo stop' surgery or ilioinguinal/iliohypogastric nerve (along anterior superior iliac spine (ASIS) and navel)for inguinal hernia repair.

9.3 Packaging and Labeling

Packaging and labeling of the IMP will be carried out by the Sponsor according to the randomization list and to European GMP Annex 13, February 2010 revision.Labeling in local language will be applied in such a way that it should not obscure the original label. The labels will be provided with a tear-off portion to be attached to the appropriate investigational product administration form. All related instructions for the investigator will be provided in the IMP Manual.

9.4 Accountability And Compliance

It is the investigator/institution's responsibility to make all reasonable efforts to assure that:

- Trial-specific product delivered to the site are correctly received (the CRO clinical trial monitor will collect the signed and dated receipt form);
- study medication is handled in a safely and properly manner and it is stored in a secured area;
- study medication is administered to participants in accordance with the protocol requirements

IMP will be administered to subjects only by authorized personnel (Principal Investigator, Co-Investigators and nurses under the Principal Investigator direct responsibility).
Drug inventory and accountability records will be kept by the Investigator or by the Pharmacist, or other authorized person.
To ensure adequate records, all study medication will be accounted for in the case report form and drug accountability inventory forms. The inventory will include details of the received and used study medication.
At the end of the study, used, unused and partially used supplies of test and reference investigational products provided by the sponsor/manufacturer will either be destroyed on site (upon written authorisation) or returned to the sponsor/manufacturer, after assessment of drug accountability.
This being an IMP intended to be used only once, as a pre-surgical treatment and therefore destined to be administered only by study staff at clinical site, no compliance issues are foreseen.
In order to allow traceability of the performed operations, before administration the investigator will have to record on the e-CRF the relevant IMP code and batch number, as well as the date and time of administration.

9.5 IMP dispensing to patients

This being an IMP intended to be used only once, as a pre-surgical treatment and therefore destined to be administered only by study staff at clinical site, no dispensing to patients is foreseen.

9.6 Other drugs to be used in the study

9.6.1. Premedication before surgery

Patients will be pre-treated with:

- Midazolam: will be given for oral administration, only in patients > 6 months of age, 45 min before surgery according to local routine practice.
- Sevoflurane by inhalationwill be given,as recommended by local routine practice,in order to induce general anaesthesia,after midazolam sedation and before IMP administration. Patients will breath unaided and, unless necessary as an emergency measure, they are not supposed to be intubated in the frame of this preoperative procedure.

9.6.2. Rescue anesthesia during surgery

Sensory block will be assessed by pin-prick test after chloroprocaine injection. In case of incomplete sensory block (when readiness for surgery not reached), fentanyl by IV injection will be given, at the dosage indicated by local routine practice, as rescue anaesthesia. All details about the administration of the rescue anesthesia will have to be recorded on the relevant CRF.

9.6.3. Rescue analgesic treatment

Paracetamol, oral or suppository, is allowed for rescue analgesic treatment after home discharge

9.7 Concomitant medications

9.7.1. Allowed medications

Any medications (other than those excluded by the clinical protocol in the section 9.7.2 below) that are considered necessary for the patients' welfare and will not interfere with the trial medication may be prescribed during the study at the Investigator's discretion.
The Investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the eCRF.
Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration and indication of each drug.
Hormonal contraceptives for females of childbearing potential are permitted.

9.7.2. Not allowed medications

The use of any of the medications listed below is not permitted during the study:

- Vasopressors;
- Ergot-type oxytocic ;
- Sulphonamides;
- Mixtures of local anaesthetics;
- Opioids;
- Antidepressants;
- Anticonvulsants;
- Antiarrhythmic drug class III, such as amiodarone;
- Strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin.

10.SAFETY AND PHARMACOVIGILANCE

A Comprehensive assessment of any apparent toxicity experienced by the participants will be performed throughout the course of the trial, from the time of the patient's signature of informed consent to the end of the observational period at day 7 (-1/+2)/2nd telephone FU. Trial site personnel will report any adverse event (AE), whether observed by the Investigator or reported by the patient/caregiver.

The safety profile of the Investigational Medicinal Product will be assessed through the recording, reporting and analyzing of baseline medical conditions, adverse events, physical examination findings including vital signs and ECG.
Adverse events will be recorded after the subject has signed the study Informed Consent, at V2 and at the two telephone Follow Up calls.
All relevant details are provided in the following sections 10.1 – 10.5.

10.1 Adverse Event definition

An Adverse Event (AE) is any symptom, sign, illness or experience that develops or worsens inseverity during the course of the study. Intercurrent illnesses or injuries should be regarded asAdverse Events. Abnormal results of diagnostic procedures are considered to be Adverse Events ifthe abnormality:

- results in study withdrawal;
- is associated with a serious Adverse Event;
- is associated with clinical signs or symptoms;
- leads to additional treatment or to further diagnostic tests;
- is considered by the investigator to be of clinical significance.

10.2 Serious Adverse Event

Adverse Events are classified as serious or non-serious. A Serious Adverse Event is any AE that is:

- fatal;
- life-threatening;
- requires or prolongs hospital stay;
- results in persistent or significant disability or incapacity;
- a congenital anomaly or birth defect.

All Adverse Events that do not meet any of the criteria for serious should be regarded as nonseriousAdverse Events.

10.3 Adverse Event Reporting Period

The study period during which Adverse Events must be reported is normally defined as the periodfrom the initiation of any study procedures to the end of the study treatment follow-up.
The Investigator/coordinator must report all adverse experiences (AEs) that occur throughout the study according to the appropriate procedures listed below. If the Investigator becomes aware of any possible Serious Adverse Event (SAE), including death, he/she must report this event by phone and fax/email the SAE form to the study sponsor within 24 hours of notification of the event.

10.4 Recording of Adverse Events

At each contact with the subject, the Investigator must seek information on Adverse Events byspecific questioning and, as appropriate, by examination. Information on all Adverse Events should be recorded immediately in the source document, and also in the appropriate Adverse Event moduleof the appropriate e-CRF form. All clearly related signs, symptoms, and abnormal diagnosticprocedures results should recorded in the source document, though should be grouped under onediagnosis.

All Adverse Events occurring during the study period must be recorded. The clinical course of eachevent should be followed until resolution, stabilization, or until it has been determined that the studytreatment or participation is not the cause. Serious Adverse Events that are still ongoing at the endof the study period must be followed up to determine the final outcome. Any Serious Adverse Eventtthat occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.5 Reporting of Serious Adverse Events

The pharmacovigilance will be under the control of the Sponsor,Sintetica SA. Any Serious Adverse Event must be reported to the study sponsor by telephone within 24 hours of theevent. A Serious Adverse Event (SAE) form must be completed by the Investigator and faxed to theStudy Sponsor within 24 hours. The Investigator will keep a copy of this SAE form on file at thestudy site. Report Serious Adverse Events by phone and fax/email to:
Phone: +41(0)91.640.42.50
email: Corporate_drug_safety@sintetica.comAt the time of the initial report, the following information should be provided:

1. Study identifier;
2. Study Center;
3. Patient number;
4. A description of the event;
5. Data of onset;
6. Current status.

Within the following 48 hours, the investigator must provide further information on the SeriousAdverse Event in the form of a written narrative. This should include a copy of the completedSerious Adverse Event form, and any other diagnostic information that will assist the understandingof the event. Significant new information on ongoing Serious Adverse Events should be providedpromptly to the Study Sponsor.

11.STATISTICAL METHODOLOGY

11.1 Rationale for sample size calculation

The size of this study is based on the A'Hern method for single stage phase II designs (35).
We estimate as satisfactory a success rate of around 90% (p1=90%) or more, while a success rate of 80% (p0=80%) or less will be considered inadequate; following the A'Hern formula based on the exact binomial distribution and assuming an 80% power and alpha=0.05, the required sample size, for each group, is 82, with 72 being the minimum required number of successes to observe in order to reach a conclusion in favour of the treatment's efficacy.
Expected drop out rate for the primary endpoint is low given that a single dose injection is requested, and assuming a 5% drop out rate 87 patients in each study arm shall be enrolled. In total 174 patients will be enrolled.
In case of successful interim analysis we could consider, based on the same article and no other modifications in the hypothesis, a mayor power of 90%. In this case the required sample size for each group

is 112 (97 success to observe) considering the drop out rate the patient enrolled in each arm are 118. In total 236 patient will be enrolled

Success rates and 95% CI will be presented separately for the two treatment groups, while a direct comparison will not be the focus of this study.

11.2 Study endpoints

11.2.1 Primary efficacy endpoint

The primary efficacy endpoint of the study will be represented by the overall proportion of patients, in each of the two dosage level groups, not requiring rescue anesthesia during surgery.

11.2.2 Secondary efficacy endpoints

The secondary efficacy endpoints of the trial will be evaluated, unless otherwise specified, on the two dosage level groups separately and, in both the two dosage level groups, on the two surgical procedures. Secondary efficacy endpoints will be:

- Proportion of patients, in both of the two dosage level groups, not requiring rescue anaesthesia (fentanyl) during the two surgical procedures separately;
- Time to onset of sensory block, defined as the time period from completion of the injection (time 0 min) to the achievement of complete sensory block,assessed by pin-prick test associated with heart rate measurement and evaluated for both surgeries;
- Time to regression of motor block evaluated in ‘calcaneo stop’ surgery only and assessed by a grade I of the standard Bromage scale (i.e. free movement of legs and feet). This evaluation will be performedimmediately after the awakening and it will be repeated 30 minutes, 1 hour, 2 hours and 3 hours after the first evaluation,as well as during the visit for discharge
- Pain intensity evaluated five times in the first 3 hours after patient’s awakening and during the home discharge visit (V2). Post-surgery assessment will be performed immediately after the awakening and it will be repeated 30 minutes, 1 hour, 2 hours and 3 hours after the first evaluation. The technique and appropriate scale for pain measurement are age-dependent therefore, different tools will have to be used for the evaluation:
  - COMFORT scale for patients <2 months of age;
  - FLACC scale for patients aged ≥ 2 months ≤ 6 years;
  - Wong-Baker scale for patients over 6 years of age;
- Time to eligibility for home discharge, defined as: “the time elapsed from completion of surgery to the time when criteria for discharge are met, regardless if the patient will be discharged from the hospital at a later time, according to the hospital procedures”. The criteria for discharge will be defined according with the Pediatric Post Anesthesia Discharge Scoring System (Ped-PADSS)
- Time from completion of IMP injection to rescue anaesthesia, whenever required
- Posology of rescue anaesthesia, whenever required
- Proportion of patients requiring additional analgesia after surgery, other than paracetamol 15 mg/kg i.v. administered during the surgery as per hospital’s standard procedures
- Type and posology of rescue analgesia required during the 7 days after surgery for each one of the two surgical procedures

11.2.3 Secondary safety endpoints

The secondary safety endpoints of the trial will be evaluated on the two dosage level groups separately and, in both the two dosage level groups, on the two surgical procedures, and will be:

- Patient general recovery, evaluated by the Investigator through the evaluation questionnaire on the day of the intervention
- Patient general recovery, evaluated by the Investigator or his deputy through the F.U 24 H evaluation questionnaire on the day after intervention
- Patient general recovery, evaluated by the Investigator or his deputy through the F.U 7-day evaluation questionnaire 7 days after intervention
- Overall proportion and 95% CI of patients with prolonged post-operative temporary loss of sensation and/or motor activity
- Vital signs at rest (heart rate, systolic/diastolic blood pressure, respiratory rate, body temperature)
- Proportion of patients with AE, in each of the two dosage level groups and in the two surgical procedures
- Summaries of adverse events (AEs), including pain at injection site, neurological symptoms (such as: convulsion) and cardiac symptoms (such as bradycardia and heart failure etc.) evaluated, during surgery, after IMP injection

11.3 Analysis sets

The analysis of study medication efficacy and safety will be performed on two study populations: Intention to Treat (ITT; all all randomised patients who fulfil the study protocol requirements in terms of study anaesthetics administration) and Per Protocol (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).

11.4 Description of statistical analysis

11.4.1 Handling of missing data

Missing data will be replaced by single imputation method (Last Observation Carried Forward (LOCF) which, in the present case, is adequate since the IMP is given only once to each participant and the overall observation period of each patient is limited to 7 days after administration of the investigational treatment.

11.4.2 Primary efficacy variable

Overall proportion of patients, in each of the two dosage level group, non-requiring additional anaesthesia for the duration of the surgical procedure will be presented together with 95% CI.

11.4.3 Secondary efficacy variables

Given the exploratory nature of the study, statistical evaluations will be mainly descriptive.
Quantitative secondary endpoints will be summarized by means of descriptive statistics as total number of evaluated subjects, mean, standard deviation, 95% confidence interval, median, minimum and maximum and number of missing values.

Categorical measures will be reported as frequency, percentages of observed values and 95% confidence interval.

11.4.4 Safety variables

Quantitative safety endpoints will be summarized by means of descriptive statistics as total number of evaluated subjects, mean, standard deviation, median, minimum and maximum and number of missing values.
Categorical safety endpoints will be reported as frequency and percentages of observed values.
AEs will be represented by frequency and percentage of patients with AE; AE will be summarized by the MedDRA System Organ Class (SOC) and Low Level Term (LLT), when calculating the number of AEs within each SOC and LLT, each subject will only be counted once.

11.5 Interim Analysis

An interim analysis for efficacy and safety is foreseen when 87 patients (half of the expected study population) will have performed the second telephone follow up and completed the study.

12.REGULATORY AND ETHICAL ISSUES

12.1 Compliance With Regulations Applicable To Clinical Trials

The study will be conducted according to the laws, regulations and administrativeprovisionsrelating to the implementation of Good Clinical Practice in the conduct ofclinical trials on medicinalproducts for human use, as applicable by nationallegislation and EU Directives. The Investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trialprotocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects whose written informed consent has been properly given are included into the trial.

12.2 Informed Consent and Child Assent Form

A minor subject should not enter in a clinical study until the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor.Parents or legal representative have been properly informed and have freelygiven his/her consent by signing and dating two (2) original copies of the Informed Consent prior toperforming any study related procedures.One original copy will be given to the parent or legal representative and the second one will be maintened at the site,following the signature and dating by the Investigator.
A copy of the proposed consent form must be submitted to the Ethics Committee (EC), togetherwith the Protocol, and other relevant documents for approval.
Each parent or legal representative’s signed Informed Consent must be kept on file (in the study filesor patient file) by the Investigator for Regulatory Authorities inspection at any time.

Study participants who, according to the investigator's judgement, are old enough to understand what the study involves (predictable between the ages of 7 and 17) will be given the opportunity to assent to the study by means of a simple (no more than one page) document (in addition to the parental consent form) which will be written in a language appropriate to the child's age. This document shall be submitted to the IRB/EC for approval together with the parental ICF and will comply with relevant local requirements of each participating country/site.

12.3 Criteria for patient's withdrawal

Participants will be free to discontinue the trial at any time without giving their reasons. A participant must be withdrawn in the event of any of the following:

- withdrawal of the subject's consent.
- discovery of ineligibility
- administrative reasons

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible. In case of premature withdrawal from the trial, the investigations scheduled for the last visit should be performed, if possible with focus on the most relevant assessments.In any case, the appropriate eCRF section must be completed.

12.4 Withdrawal from the Investigational Medicinal Product

Not applicable (single-dose study)

12.5 Premature discontinuation of the trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, e.g. due to:
  - Evidence of inefficacy of the IMP,
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - Other unfavorable safety findings.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's IMP.
- Withdrawal of IMP(s) from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations. The whole trial may be terminated or suspended upon request of Health Authorities.

12.6 Definition of end of the trial

The study will terminate once all the enrolled participants (with the exception of properly documented drop-out and lost to follow up) will have performed the telephone follow up call n. 2 (Day 7).

12.7 Regulatory Authorities and Ethics Committee (EC)

The present protocol is part of an extensive Pediatric Investigational Plan (PIP) which has been submitted to the Paediatric Committee (PDCO) of the European Medicine Agency (EMA).The PDCO has adopted a positive opinion on both the overall research strategy and on the present clinical protocol.
Before starting with the study operations, the clinical protocol must be approved in writing by an appropriate EC.Any amendments to the Protocol or subsequent changes to the Informed Consent as a result ofchanges to the Protocol, must be approved by the EC. Records of the EC review and approval of alldocuments pertaining to this study must be kept on file by the Investigator and are subject toRegulatory Authorities inspection during or after completion of the study. Unexpected andassociated SAEs must also be reported to the EC.

12.8 Protocol Amendments

Changes to the Protocol should only be made by an approved protocol amendment.Protocol amendments must be approved by the Sponsor, Central EC and/oreach respectivesite's EC (if applicable), prior to implementation.

12.9 Patient Confidentiality

The Sponsor is concerned about the individual patient's privacy and, therefore, all patient data willbe identified only by a subject identification number and subject name and date of birth code. Thedata will be blinded correspondingly in all data analysis.
However, it is required that the Investigator will permit, after receiving patient's approval, the studymonitor, independent auditor or regulatory agency personnel (with or without the Investigator) to review that portion of the patient's medical record that is directly related to the study.

12.10 Clinical Trial Insurance

Adequate insurance coverage for all subjects of all countries participating in the trial will be supplied by the Sponsor. Insurance conditions will meet the relevant local laws and regulations.

13.DOCUMENTATION

13.1 Site Documents Required

Prior to the initiation of the study, the following items must be received by the Sponsor:

1. Letter of EC approval for the Protocol, amendments (if applicable), Informed Consent,advertisements (if applicable), Membership list;
2. A signed copy of the Protocol, amendments and notifications (if applicable);
3. The Investigator's curriculum vitae as well as the curriculum vitae of any Co-Investigator(s);
4. A list of the persons involved with the study and their signatures;
5. Study site agreement(s);
6. Health regulatory approval (where applicable);
7. Local laboratory certification and normal ranges (if applicable).

13.2 Site Documents Supplied By The Sponsor

Prior to the initiation of the study, the Sponsor will supply the Investigator with the following itemsin addition to the Protocol:

1. Procedure and credential for the access to the electronic Case Report Forms;
2. Operations Manual (inclusive of e-CRF manual);
3. Model of Informed Consent;
4. Current version of the Investigator's Brochure and/or Product Monograph;
5. Regulatory Binder
6. IMP Manual.

13.3 Maintenance And Retention Of Records

The Study will be conducted according to Good Clinical Practices. It is the responsibility of theInvestigator to maintain a comprehensive and centralized filing system of all relevantdocumentation. All original subject files (medical records) must be stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator will be instructed to consult with the Sponsor before disposal of any study recordand to notify the Sponsor of any change in the location, disposition or custody of the study files.

13.4 Case Report Form (Crf)

Electronic CRFs (eCRFs) for individual patients will be used in the frame of this study.eCRFs are used to record study date and are an integral part of the study and subsequent reports.It is the Investigator's responsibility to ensure the accuracy and completeness of the data entered in the eCRFs. The data will be entered into a validated database. CRO Data Managementwill be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control procedure, and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.
Source documents for this study such as the clinic chart or tests are to be maintained in a studybinder.eCRFs, source documents and copies of test results must be available at all times for inspection bythe study monitor, Sponsor, CRO and Regulatory Authority.

13.5 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's and parents' (or tutor's) full name,
- Date of birth,
- Sex,
- Height,
- Weight,
- Medical history and concomitant diseases,
- Prior and concomitant therapies (including changes during the trial),
- Trial identification (Sponsor's trial number according to clinical trial protocol),

- Date of subject's inclusion into the trial (i.e. date of giving informed consent),
- Subject number in the trial,
- Dates of the subject's visits to the site and of telephone follow-up calls,
- Any medical examinations and clinical findings predefined in the clinical trial protocol,
- All adverse events observed in the subject,
- Date of subject's end of trial,
- Date of and reason for early withdrawal of the subject from the trial or from IMP, if relevant.

It must be possible to identify each subject by using this subject file. Additionally, any other documents containing source data must be filed (e.g., ECG trace and report, completed scales and questionnaires). Such documents must bear at least the subject number and the date when the procedure was performed.

13.6 Monitoring

The study monitor will be responsible for coordinating the activities of the study monitoring team toensure adherence to ICH guidelines and the standard operating procedures.Experienced Monitors from CRO will be trained to monitor the study. The Monitors will be trainedon ICH GCP Guidelines, trial-specific SOPs, study protocol and the study monitoring convention.
These visits are for the purposes of verifying adherence to the Protocol and the completeness andexactness of data entered on the eCRF. The study monitor will verify eCRF entries by comparingthem with the primary source document which will be madeavailable for this purpose. The Monitor will review the progress of the study with the Investigatorand other site personnel on a regular basis. At the end of the study, a Closure Monitoring Visit willbe performed. Monitoring visits will be arranged in advance with site personnel at a mutuallyacceptable time. Sufficient time must be allowed by the site personnel for the Monitor to reviewCRFs and relevant source documents. The Coordinator and/or Investigator should be available toanswer questions or resolve data clarifications. Adequate time and space for these visits will bemade available by the Investigator.

13.7 Protocol Modifications

The procedures defined in the Protocol and in the e-CRFs will be carefully reviewed to ensure that allparties involved with the study fully understand the Protocol. In order to ensure the validity of thedata, with minimal exceptions, no deviations from the Protocol may be made unless waived by theSponsor depending upon the magnitude of the deviation. If the issue is broad enough to warrantrevision of the Protocol, such revisions must be submitted to and have approval in writing from theSponsor, and the EC prior to implementation at the site.

13.8 Audit/Inspection

The study may be inspected by regulatory agencies. These inspections may take place at any timeduring or after the study and are based on the local regulations.The purpose of the Audit is to determine whether or not the study is being conducted and monitoredin compliance with recognized GCP guidelines or laws and study protocol.

14.USE OF INFORMATION AND PUBLICATION

14.1 Confidential Information

Confidential information refers to any information provided by the Sponsor. This includes,but is not limited to, the clinical protocol (and protocol amendments, if any), eCRFs, assay or studymethods and basic scientific data. Any data collected during the study should also be consideredas confidential.

14.2 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH Topic E3 will be written by the Sponsor/CRO.

14.3 Publication policy

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.
The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

15.INVESTIGATOR'S AGREEMENT

I have carefully read the foregoing Protocol and agree that it contains all the necessary informationfor conducting this study safely. I will conduct this study in strict accordance with this Protocol andwill attempt to complete the Study within the time designated.
I will provide copies of the Protocol and all other information to all personnel responsible to mewho participate in the study. I will discuss this information with them to assure that they areadequately informed regarding the drugs and conduct of the study.
I agree to keep records on all subject information (CRFs, shipment and drugs return forms and allother information collected during the study) in accordance with GCP and local regulations.

_____	_____
Investigator's signature	Sponsor signature
Date: _____	Date: _____
Name _____	Name_____
(please use capital letters or stamp)	(please use capital letters or stamp)

PROTOCOL TITLE
Randomized, multi-center, double-blind, two-armed, parallel active groups, prospective trial, to evaluate, in pediatric population undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, the efficacy and safety of chloroprocaine 1% and 2% for peripheral nerve block based on concentration–response relationships.

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17. LIST OF APPENDICES

17.1 Declaration of Helsinki

17.2 FLACC scale (sample)

17.3 COMFORT scale (sample)

17.4 WONG-BAKER scale (sample)

17.5 Questionnaires(24h – 7days)

17.6 Patient diary