STATISTICAL ANALYSIS PLAN

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.

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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	Invetsigational Medicinal Product
IVRA	Intravenous Regional Anaesthesia
LA	Local Anesthetic
LAST	Local Anesthetic Systemic Toxicity
LLT	Low Level Term
MedDRA	Medical Dictionary for Regulatory Activities
PNB	Peripheral Nerve Block
RA	RegionalAnesthesia
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
USA	United States of America

1. Introduction

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. Objectives

2.1 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 anesthesiaduring surgery.

2.2 Secondary Objectives

The secondary objectives of the study is to evaluate the efficacy and safety e of the trial. It 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

3. Investigational Plan

3.1 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 listed in Appendix 17.6.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 HCl will 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 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.

Immediately after the end of the surgical intervention, all patients will be administered Paracetamol 15 mg/kg, i.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);

3.2 Study Endpoints

3.2.1 Primary 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

3.2.2 Secondary efficacy endpoints

- 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 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

3.2.3 Secondary safety endpoints*:*

- 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 injectionThe 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:

3.3 Treatments

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

4. General Statistical Considerations

4.1 Statistical Reporting and Analysis Convention

4.1.1 Statistical tests and Confidence Intervals Convention

Unless otherwise specified, all statistical tests will be performed using a two-sided 0,05 significance level. Differences between treatment groups will be estimated along with their two-sided 95% Confidence Intervals (CI) .P values will be presented when appropriate.

Binomial Data

For individual proportion (rates) corresponding to treatment arms the exact (Clopper –Pearson) method will be used to produce the 95% CI. Comparison of proportions between the treatment arms

will be assessed using a Fisher's exact test. Difference in proportions between the two treatment arms will be estimated and the associated confidence will be provided.

Analysis of variance (ANOVA)

An ANOVA model will be constructed with the treatment arm and country as fixed effects . The adjusted means in each treatment arm and the adjusted mean difference between treatment arms will be displayed with the corresponding two sided 95% CI For the primary analysis only, the assumption of Normality underlying the ANOVA model will be tested, as described in section 8.1.1

4.1.2 Treatment Naming Conventions

Unless otherwise specified, summaries and analysis will be provided by treatment arm using the following convention. The total group will be presented where appropriate

Arm 1 ChloroprocaineHCl 1% injection (10 mg/mL)

Arm 2 ChloroprocaineHCl 2% injection (20 mg/mL)

In addition where specified results will be provided separately

4.1.3 Table and Appendix Presentation

Continuous data will be summarized using descriptive statistics (i.e. the number of subjects with non-missing values [n], mean, standard deviation (SD), median, minimum, and maximum, and Q1and Q3 for selected parameters). For the summary statistics of all numerical variables unless otherwise specified,

- Minimum and Maximum will be displayed to the same level of precision as reported
- Mean and Median will be displayed to one level of precision greater than the data collected.
- Standard deviation will also be displayed to one level of precision greater than the data collected
- P-values will be rounded to three decimals. If a p-value is less than 0.001 it will reported as "<0.001". If a p-value is greater than 0,999 it will reported as ">0.999".

Categorical data will be described using subject count and percentage in each category. Percentages in general will be displayed to one decimal place. If the calculated percentage is >0.0% but <0.1% then <0.1 will be presented in the relevant table and/or listing. If the frequency count is zero, the percentage will be suppressed in order to draw attention to the non-zero counts. In addition, in summary tables including categorical data, all categories presented on the Case Report Form (CRF) (e.g. discontinuation reason), or all categories in an ordered interval(e.g. age groups), will be displayed regardless of whether or not a subject is found in a given category. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and

missing values. The denominator for all percentages will be the number of subjects within the analysis set of interest, unless otherwise specified.

For other categorical data (e.g. AEs and medications), only categories with at least one subject will be presented.

Unless otherwise specified , differences between the treatment groups will be computed as arm 1 (ChloroprocaineHCl 1%) versus arm 2 (ChloroprocaineHCl 2%).

All analysis will be conducted using ..... . All summary statistics will be rounded. The rounding rules described previously in this section are summarized in Table 1 below

The tables will be accompanied by data appendices sorted by subject number. Subjects are uniquely identified by a concatenation of study country number, centre number and subject number . All data available from the eCRFs along with any derived variables will be listed.

When no data are available for a table or appendix, an empty page with the title will be produced with suitable text (e.g. “there are no observations for this table/appendix”)

Statistic/Parameter	**Number of decimal places used for reporting**
Counts (n)	None
Percentages (%)	1 decimal place *Note : if the calculated percentage is >0.0 but<0.1%then <0.1%is to be presented in the relevant table and/or listing. Percentages are not presented for 0 count*
Mean	Raw data + 1 decimal place
Median	Raw data + 1 decimal place
SD	Raw data + 1 decimal place
First quartile (Q1)	Raw data + 1 decimal place
Third quartile (Q3)	Raw data + 1 decimal place
Confidence intervals	Raw data + 1 decimal place
Minimum	Same as raw data
Maximum	Same as raw data
Coefficient of Variance (CV)%	1 decimal place
p-values	3 decimal place

Table 1 Precision Rules for Reporting

4.1.4 Definition of Visit Windows

No visit windows will be applied unless otherwise specified.

In general unscheduled visit will be not included in by visit summaries, however unscheduled assessment will contribute to calculation of derived/imputed variables (where applicable). Unscheduled measurements will be evaluated case by case during the Data Review Meeting and the decision will be fully documented in the Data Review Report.

Listing will include scheduled and unscheduled data.

Early termination data will be mapped to the next available visit number.

The following visit label (see Table 2) will be used for the Tables and Listings

Study Visit Number	Analysis Time Point
V1	Screening
V2	Surgery and Discharge
V3	FU Day 1
V4	FU Day 7

Table 2 Visit Labels

4.2 Sample Size

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.

4.3 Randomization, 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.

4.3.1 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
All the data collected will be reviewed, finalised and documented during the Data Review Meeting that will be held prior to database lock.

4.4 Analysis Sets

Membership of the analysis sets will be reviewed and agreed at the Data Review Meeting before the database lock and decisions will be fully documented in the Data Review Report

The analysis sets that will be used in this study are defined below

4.4.1 Intention to Treat (ITT)

The ITT set will include all randomized subjects fulfill the study protocol requirements in terms of study anesthetics administration

4.4.2 Per Protocol (PP)

The PP set will include all randomized subjects fulfill the study protocol requirements in terms of study anesthetics administration and primary efficacy evaluation, with no major deviation that could affect the primary efficacy results).

5. Subject Disposition

5.1 Disposition

Subject disposition of screening failures will be summarised for the ENR set . A disposition of subjects includes the total number of subjects randomized and the total number of subjects who failed screening. The percentages will be based on the number of subjects enrolled. The reasons for discontinuation for screening failures will also summerised in this table as recorded on the CRF. The percentages will be based on the number of screen failures. All results for screen failures will be displayed only for the total column.

Subject disposition data will be presented in a listing

A summary of the analysis sets based on the ENR set will include the number and the percentage of subjects for the following categories: all enrolled patients, subjects in ITT set, subjects in PP set. All result will be presented by treatment arm , type of surgery and overall.

5.2 Protocol Deviations

Subjects with major and minor protocol deviations will be listed and summarised by treatment group type of surgery and overall using the ITT Set.

All protocol deviations will be identified prior the database lock and a clinical/medical judgment will be necessary to classify each violation as “major” or not. A major protocol violation is defined as a protocol deviation that is considered to have a significant impact on the results of subject. The exact definition of major and minor protocol deviation will be discussed at the data review meetings and documented in the Data review Report . As a general principle, major deviations will include the following categories:

a) Subjects who do not satisfy key inclusion or exclusion criteria
b) Subjects who require a medication that is prohibited by protocol
c) Subjects who had a randomization error and received incorrect trial treatment
d) Other major protocol violations that may identified during data review (for example assessment performed outside the allowed time windows, study procedure deviation etc.)

All subjects with major protocol deviations will be excluded from the PP Set, as per the PP Set definition provided in Section 4.4.3

Additional protocol deviations may be identified and documented during the Data Review Meeting prior the database lock

Number and percentages of subjects with at least one major or minor protocol deviation during the study period as well as each major or minor protocol deviation category, will be summarised by coded term , deviation term, by treatment groupkind of surgery and overall based on the ITT Set.

Mayor and minor protocol deviation data will be provided in separate listings

6. Demographics and Baseline Characteristics

6.1 Demographics

A summary of demographics and baseline information will be presented. The demographics characteristics consist of :

- Age (years)
- Age group (0 to 27 dd;28dd to 23 mm;2 to 6yy; 6 to 11yy; 12 to 18yy)-
- Sex

A subject's age in year will be calculated using the date of the informed consent and the date of birth and the date of birth as integer part of formula (Date of Informed consent – date of birth +1)/365.25. In cases where Date of Birth is not collected due to local country regulations, the aged collected in the eCRF will be used.

The Baseline characteristics consist of

Baseline height (m)

Baseline weight (kg)

BMI (kg/m2)

Height: in children younger than two years, body length should be measured 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

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.

Age (years), baseline height (m), baseline weight (kg), and baseline BMI (kg/m2) will be summarized using descriptive statistics. The number and percentage of subjects by age category, sex(male, female) and BMI category () will be also reported. Percentages will be based on the total

number of subjects in the ITT Set and presented by treatment arm and overall. The above summaries will be repeated for the PP set.

Subject demographic and baseline characteristics will be presented in a listing.

6.2 Medical History

Medical History and Concomitant Disease are collected at screening using the same ECrf and will be coded using Medical Dictionary for Regulatory Activities (MedDRA) versionXX

6.2.1 Medical History and Concomitant Disease

Medical history and concomitant disease will be summarised by treatment arm and overall, without inferential statistics.

Medical history includes any significant condition or diagnoses reported as having resolved prior to visit 1 (Screening visit)

Concomitant diseases are significant conditions or diagnoses reported with an end date after informed consent date or identified as ongoing at visit 1(Screening visit)

The number and percentage of subjects with any medical history or concomitant diseases will be summarized overall and for each System Organ Class (SOC) and Preferred Term (PT). if a subject has more than one condition coded to the same PT , the subject will be counted only once for that PT. Similary, subjects reporting multiple conditions within the same SOC will be counted only once for that SOC.
All summaries will be performed using ITT
Subject medical history and concomitant diseases data including specific details will be presented in a listing

6.2.2 Inclusion and Exclusion Criteria

A listing of inclusion criteria that were not met and of exclusion criteria that were met for all visit will be listed by subject.

7. Treatments and Medications

7.1 Prior , Maintained, Concomitant and Post-Treatment Medications

All medications will be coded according the World Health Organization (WHO) drug dictionary (WHODRUG December 2014)

- A prior medication is defined as any medication that has an end date prior to the date of the first dose of study drug
- A maintained medication is defined as any medication that has start date before the date of the first dose of study drug and has an end date on or after the date of first dose of study drug (or identified as ongoing)
- A concomitant medication is defined as any medication that has a start date that is on or after the date of first dose of study drug and before or on the date of the last dose of study drug(or identified as ongoing at the end of the study)

- A post-treatment medication is defined as any medication that has a start date that is after the date of last dose of study drug.

For the purpose to identifying if a medication is a prior, maintained, concomitant and/or post-treatment medications , incomplete medication start and stop dates will be imputed as follows:

Missing start dates(where UK, UKN,UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY , assume 01 –MMM-YYYY
- DD-UKN-YYYY e UK –UKN-YYYY assume 01-JAN YYYY

Missing start dates(where UK, UKN,UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY , assume the last day of the month
- DD-UKN-YYYY e UK –UKN-YYYY assume 31-DEC YYYY

If start date is completely missing and end date is not prior of the first dose, then the medication will be classified as maintained and concomitant. Medications for which the start and end dates are missing will be classified as prior, maintained and concomitant medications

7.1.1 Prior Medication

The number and percentages of subjects with at least one prior medication will be summarized without inferential statistics, by treatment arm and overall
All summaries will be performed using ITT set

7.1.2 Maintained Medication

The number and percentages of subjects with at least one maintened medication will be summarized without inferential statistics, by treatment arm and overall
All summaries will be performed using ITT set

7.1.3 Concomitant Medication

The number and percentages of subjects with at least one Concomitant medication will be summarised without inferential statistics, by treatment arm and overall
All summaries will be performed using ITT set

7.1.4 Post-Treatment Medication

The number and percentages of subjects with at least one Post-Treatment medication will be summarised without inferential statistics, by treatment arm and overall
All summaries will be performed using ITT set

7.2 Study Treatment

A brief decscription of the precise treatment drug administrated in each treatment arm, including mode of administration and dose can be found in section 3.3 of this document

8. Efficacy Analysis

The primary analysis set for efficacy analysis will be the ITT set. Supportive analysis will be performed on the PP set .

8.1 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.
The overall proportion will be calculated first for ITT set (number of patients not require rescue anesthesia /number of population of ITT Set) and than for PP set (number of patients not require rescue anesthesia /number of population of PP Set)

8.2 Secondary Efficacy Endpoint

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.

8.2.1 Ratio between surgery

Proportion of patients, in both of the two dosage level groups, not requiring rescue anaesthesia (fentanyl) during the two surgical procedures separately;

8.2.2 Time to onset of sensory block

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;

8.2.3 Time to regression of motor block

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

8.2.4 Pain intensity

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 score will be summarised using descriptive statistics overall, by treatment, by surgery. 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)

The COMFORT Scale is a pain scale that may be used by a healthcare provider when a person cannot describe or rate their pain.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.

FLACC scale (for patients aged ≥ 2 months ≤ 6 years);

FLACC stands for face, legs, activity, crying and consolability. The FLACC pain scale was developed to help medical observers to assess the level of pain in children who are too young to cooperate verbally. It an also be used in adults who are unable to communicate.
The FLACC scale is based on observations made regarding the patient's face, the position of their legs, their actions, and whether they are calm or consolable. Zero to two points are assigned for each of these 5 areas of observation.
The overall score is recorded as follows:
0= Relaxed and comfortable
1-3= Mild discomfort
4-6= Moderate pain
7-10 = Severe discomfort/pain
By recording the FLACC score periodically, the medical personnel can gain some sense of whether the patient's pain is increasing, decreasing or stable.

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

The Wong Baker Faces Pain Scale 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. A numerical rating is assigned to each face, of which there are 6 total.

8.2.5 Time to eligibility for home discharge

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 Anaesthesia Discharge Scoring System (Ped-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 anaesthetist before discharge; no requirement wish of the anaesthetist to see parents or child before discharge.

8.2.6 Time to rescue anaesthesia (whenever required)

Time from completion of IMP injection to rescue anaesthesia, whenever required

8.2.7 Posology of rescue anaesthesia (whenever required)

Posology of rescue anaesthesia, whenever required

8.2.8 Proportion of patients requiring additional analgesia after surgery

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 (number of patient requiring additional/number of patient)

8.2.9 Posology of requiring additional analgesia after surgery

Type and posology of rescue analgesia required during the 7 days after surgery for each one of the two surgical procedures.

The number and percentage of subjects will be tabulated by treatment arm,

9 Safety Analysis

All Analysis of safety will be conducted using ITT Set, unless otherwise specified, the safety data will be summarised by treatment arm, and surgery as appropriate.
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

9.1 Adverse Event

The definitions an AE, ADR, Serious AE (SAE) and serious ADR (SADR) are provided in detail in the protocol Section 10
An ADR is an "untoward and unintended response to an investigational medicinal product related to any dose administered " All adverse event judged by either the reporting Investigator or the Sponsor as having a reasonable casual relationship to a medicinal product qualify as adverse reaction. The expression "reasonable casual relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a casual relationship. This is captured in the CRF as an AE positively identified as having " a reasonable possibility of relatedness to study drug"
The following definitions will be used for AE analysis purposes.
A treatment-emergent AE (TEAE) is defined as an AE that begins on or after the first dose of study drug.
A Pre-treatment emergent AE (PTEAE) is defined as an AE that begins on or after the informed consent and before the first dose of study drug
For the purpose of inclusion
Missing start dates(where UK, UKN,UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY , assume 01 –MMM-YYYY
- DD-UKN-YYYY e UK –UKN-YYYY assume 01-JAN YYYY

Missing end dates(where UK, UKN,UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY , assume the last day of the month
- DD-UKN-YYYY e UK –UKN-YYYY assume 31-DEC YYYY

All TEAEs will be summarised as described in the following sections, as well as presented in listings. PTEAEs will only be presented in listings

9.1.1. Overview of Adverse Event

An overview summary of the number and percentage of subjects with any (at least one occurrence of that event) will be presented by treatment arm for the following categories:

- TEAE
- TEADR
- Serious TEAE (TESAE)
- Serious TEADR (TESADR)
- Severe TEAE
- TEAE leading to death

In addition a summary of TEAEs will be provided by treatment arm and will be tabulated by SOC and PT. this summary will present the number of subject , associated percentage and number of events
All TEAEs will be presented in a listing.

9.1.2 Relationship of Adverse Event

A summary of TEAEs by relationship (i.e. “Related” and “not Related”) to study drug will be presented in a table by incidence of occurrence
In the TEAE relationship table, if a subject reports multiple occurrences of the same TEAE, only the related occurrence will be presented . Treatment-emergent AEs that are missing a relationship will be presented in the data listing with a missing relationship.

9.1.3 Severity of Adverse Event

A summary of TEAEs by severity that will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are “Mild”, “Moderate” and “Severe”

All TEAEs identified as “Severe” will be presented in a separate listing.

9.2 Vital Sign Measurements

Summary tables presenting observed values and changes from baseline will be presented for vitalsign data, including Systolic Blood Pressure (SBP) (mmHg), Diastolic Blood Pressure (DBP)(mmHg), temperature (°C), Pulse Rate (PR) (bpm), weight (kg) and BMI (kg/m2) by treatmentarm Blood pressure position and body temperature location will not be accounted for this analysis.

9.3 Physical Examination

Physical examination results for all subjects will be presented in a listing.

10 Pharmacokinetics

Not applicable.

11 Pharmacodynamics

Not applicable

12 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.
The sponsor will decide if this analysis will be carried out based on the progress of the enrolment.
The interim analysis, if performed, will follow the indicationsprovided above

13 Changes in the Planned Analysis

Not applicable, in this version

14. REFERENCES

1. Giorgio Veneziano, Peter Iliev, Jennifer Tripi, David Martin, Jennifer Aldrink, Tarun Bhalla, Joseph Tobias. Continuous chloroprocaine infusion for thoracic and caudal epidurals as a postoperative analgesia modality in neonates, infants, and children. Pediatric Anesthesia 26 (2016) 84–91
2. David M. Polaner, Andreas H. Taenzer, Benjamin J. Walker, Adrian Bosenberg, Elliot J. Krane, Santhanam Suresh, Christine Wolf, Lynn D. Martin. Pediatric Regional Anesthesia Network (PRAN): A Multi- Institutional Study of the Use and Incidence of Complications of Pediatric Regional Anesthesia. Anesth Analg 2012;115: 1353–64
3. Joseph D Tobias et al. Chloroprocaine for epidural anaesthesia in infabnts and children. Journal of the American association of Nurse Anesthesists, 1995(69) 2: 131 -135
4. Christopher M. Bernards, Admir Hadzic, Santhanam Suresh, Joseph M. Neal. Regional Anesthesia in Anesthetized or Heavily Sedated Patients. Regional Anesthesia and Pain Medicine, 2008(33) 5: 449–460
5. R. D. Shah and S. Suresh. Applications of regional anaesthesia in paediatrics. British Journal of Anaesthesia 2013 (111) (S1): 114– 124
6. William A. Catteral, Kennet Mackie. Goodman and Gilman's "The pharmacological basis of therapeutics" 2011. Local Anesthetics - chapt 14 (369 – 86)
7. Benjamin G. Covino, Donald B. Gjddon. Pharmacology of Local Anesthetic Agents. J Dent Res 1981. 60(8):1454-1459
8. C. L. Jeng, T. M. Torrillo and M. A. Rosenblatt. Complications of peripheral nerve blocks. British Journal of Anaesthesia 2010. 105 (S1): i97–i107
9. Kristine Henderson, Navil F. Sethna, Charles B. Berde. Continuous Caudal Anesthesia for Inguinal Hernia Repair in Former Preterm Infants. J. Clin. Anesth. 1993(5): 129 – 133
10. Joseph D Tobias et al. Continuous regional anaesthesia in infants. Can J Anaesth 1993(40) 11: 1065-1068
11. Robert M Maccani et al. Femoral and lateral femoral cutaneous nerve block for muscle biopsies in children. Paediatric Anaesthesia 1995 (5): 223 – 227
12. Tobias JD, Rasmussen GE, Holcomb GW , Brock JW , Morgan WM Continuous caudal anaesthesia with chloroprocaine as an adjunct to general anaesthesia in neonates.Can J Anaesth. 1996 Jan;43(1):69-72.
13. Joel B. Gunter. Benefit and Risks of Local Anesthetics in Infants and Children. Pediatr Drugs 2002; 4 (10): 649-672
14. P. Marhofer, C. Sitzwohl, M. Greher and S. Kapral. Ultrasound guidance for infraclavicular brachial plexus anaesthesia in children. Anaesthesia, 2004, 59, pages 642–646
15. U. Oberndorfer, P. Marhofer, A. Bosenberg, H. Willschke, M. Felfernig, M. Weintraud, S. Kapral and S. C. Kettner. Ultrasonographic guidance for sciatic and femoral nerve blocks in children. British Journal of Anaesthesia 98 (6): 797–801 (2007)
16. H. Willschke, MD, A. Bosenberg, MBChB, FFA(SA), P. Marhofer, MD, S. Johnston, MBChB, FCA(SA), S. Kettner, MD, U. Eichenberger, MD, O. Wanzel, MD, and S. Kapral, MD. Ultrasonographic-Guided Ilioinguinal/Iliohypogastric Nerve Block in Pediatric Anesthesia: What is the Optimal Volume? AnesthAnalg2006;102:1680–4
17. G. Ivan1 MD, G. Mattioli MD, M. Rega MD, A. Conio MD, V. Jasonni MD, P. De Negri MD. Clonidine-mepivacaine mixture vs plain mepivacaine in paediatric surgery. Paediatric Anaesthesia 2996 6: 111-114
18. Vrushali Ponde, Ankit P. Desai & Dipal Shah. Comparison of success rate of ultrasound-guided sciatic and femoral nerve block and neurostimulation in children with arthrogryposis multiplex congenita: a randomized clinical trial. Pediatric Anesthesia 23 (2013) 74–78
19. D. Faraoni MD et al. Does ultrasound guidance improve the efficacy of dorsal penile nerve block in children? Pediatric Anesthesia 2010 20: 931–936

20. Santhanam Suresh, MD, and Melissa Wheeler, MD. Practical Pediatric Regional Anesthesia. New concepts and techniques in pediatric anesthesia. Volume 20 • Number 1 • March 2002
21. Peter Marhofer, Giorgio Ivani, Santhanam Suresh, Estela Melman, Guadalupe Zaragoza & Adrian Bosenberg. Everyday regional anesthesia in children. Pediatric Anesthesia 22 (2012) 995–1001
22. G. Ivani, V. Mossetti. Pediatric regional anesthesia. Minerva Anestesiologica Vol. 75 - No. 10. 577-83
23. Micic S., Horvat M., Komen Usljebrka H., Frkovic V., Azman J., Poldan Grabar N. Ultrasound guided popliteal sciatic nerve block vs. multimodal analgesia for postoperative pain control following calcaneo-stop surgery in children. European Journal of Anaesthesiology 2011, 28:206
24. Vito Pavone, Luciano Costarella, Gianluca Testa, Giorgio Conte, Maria Riccioli,Giuseppe Sessa. Calcaneo-stop Procedure in the Treatment of the Juvenile Symptomatic Flatfoot. / The Journal of Foot & Ankle Surgery 52 (2013) 444–447
25. Mary L. Brandt. Pediatric Hernias. Surg Clin N Am 88 (2008) 27–43
26. Qayyum F, Alvear D (2017) Management of Inguinal Hernias in Premature Infants- Pre or Post Discharge- What Is Best? J Pediatr Neonatal Care 7(1): 00275. DOI: 10.15406/jpnc.2017.07.0027
27. Bromage PR. Epidural analgesia. W.B. Saunders Co. 1978. page 144.
28. Ambuel B, Hamlett KW, et al. Assessing distress in pediatric intensive care environments: The COMFORT scale. J Pediatric Psychology. 1992; 17: 95-109.
29. Merkel, S. I., Voepel-Lewis, T., Shayevitz, J. R., & Malviya, S. (1997). The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatric Nursing, 23(3), 293–297.
30. Wong-Baker FACES Foundation (2016). Wong-Baker FACES® Pain Rating Scale.
31. Biedermann S, Wodey E, De La Briere F et al. Paediatric discharge score in ambulatory surgery. Ann Fr Anesth Reanim 2014; 33: 330–334.
32. Moncel JB, Nardi N, Wodey E, Pouvreau A, Ecoffey C (2015). Evaluation of the pediatric post anesthesia discharge scoring system in an ambulatory surgery unit. Pediatric Anesthesia 25 (2015) 636–641
33. Chung F. Are discharge criteria changing? J Clin Anesth 1993; 5(6 Suppl 1): 64S–68S
34. Chung F. Discharge criteria – a new trend. Can J Anaesth 1995; 42: 1056–1058..
35. R. P. A'Hern, Sample size tables for exact single-stage phase II designs, Statistics In Medicine Statist. Med. 2001; 20:859-866

Tables

Disposition – Screening Failures
All Enrolled Analysis Set

	Total (N=xxx)
TOTAL NUMBER OF ENROLLED SUBJECTS n (%) XX (XX.X)	
RANDOMISED [1] XX (XX.X)	
SCREENING FAILURES [1] XX (XX.X)	
SCREENING FAILURES	
AGE (YEARS)	
n XX	
MEAN (SD) XX.X (XX.XX)	
MEDIAN XX.X	
MIN, MAX XX, XX	
AGE CATEGORIES (YEARS) n (%)[2]	
1 XX (XX.X)	
2 XX (XX.X)	
3 XX (XX.X	
4 XX (XX.X	
5 XX (XX.X	
SEX n (%) [2]	
MALE XX (XX.X)	
FEMALE XX (XX.X)	
RACE n (%) [2]	
WHITE	
ASIAN XX (XX.X)	
BLACK XX (XX.X)	
OTHER XX (XX.X)	

[1] Percentages are based on the number of all enrolled subjects.
[2] Percentages are based on the number of screen failures.

Source Data: Listing 16.2.1.1, 16.2.1.2

Table 14.1.1.1
Disposition – Screening Failures
All Enrolled Analysis Set

	Total (N=xxx)
PRIMARY REASON FOR DISCONINUATION FOR SCREENING FAILURE n (%) [2]	
REASON #1	xx (xx.x)
REASON #2 xx (xx.x)	xx (xx.x)
REASON #3 xx (xx.x)	xx (xx.x)
REASON #4 xx (xx.x)	xx (xx.x)
REASON #5 xx (xx.x)	xx (xx.x)
…	

[1] Percentages are based on the number of all enrolled subjects.
[2] Percentages are based on the number of screen failures.
Source Data: Listing 16.2.1.1, 16.2.1.2
Prog Note(s):

1. Present reasons as provided in the CRF page.

Table 14.1.1.2
Disposition
All Randomized Analysis Set

	A (N=xxx) n (%)	B (N=xxx) n (%)	Total (N=xxx) n (%)
TOTAL NUMBER OF RANDOMISED SUBJECTS	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED	xx (xx.x)	xx (xx.x)	xx (xx.x)
DISCONTINUED	xx (xx.x)	xx (xx.x)	xx (xx.x)
PRIMARY REASON FOR DISCONTINUATION			
REASON #	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON #2	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON #3	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON #4	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON #5	xx (xx.x)	xx (xx.x)	xx (xx.x)

...

Note: Percentages are based on the number of randomised subjects within each treatment group.

Source Data: Listing 16.2.1.2

Table 14.1.1.3
Disposition by country
All Randomized Analysis Set

	A (N=xxx) n (%)	B (N=xxx) n (%)	Total (N=xxx) n (%)
COUNTRY (XXX)			
TOTAL NUMBER OF RANDOMISED SUBJECTS	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED	xx (xx.x)	xx (xx.x)	xx (xx.x)
DISCONTINUED	xx (xx.x)	xx (xx.x)	xx (xx.x)
PRIMARY REASON FOR DISCONTINUATION			
REASON #	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON #2	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON #3	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON #4	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON #5	xx (xx.x)	xx (xx.x)	xx (xx.x)

…

Note: Percentages are based on the number of randomised subjects within each treatment group.

Source Data: Listing 16.2.1.2

Table 14.1.1.4
Analysis Sets
All Randomized Analysis Set

	A (N=xxx) n (%)	B (N=xxx) n (%)	Total (N=xxx) n (%)
TOTAL NUMBER OF ALL RANDOMISED SAFETY)	xx (xx.x) xx (xx.x)	xx (xx.x) xx (xx.x)	xx (xx.x) xx (xx.x)

Table 14.1.1.5
Major Protocol Deviation
All Randomized Analysis Set

	A (N=xxx) n (%)	B (N=xxx) n (%)	Total (N=xxx) n (%)
SUBJECTS WITH AT LEAST ONE MAJOR PROTOCOL VIOLATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
CATEGORY 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEVIATION 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEVIATION 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
CATEGORY 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEVIATION 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEVIATION 2	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Subjects could have more than one major protocol deviation. Percentages are based on the number of
all randomised subjects within each treatment group
Source Data: Listing 16.2.2.2
…

Table 14.1.1.6
Minor Protocol Deviation
All Randomised Analysis Set

	A (N=xxx) n (%)	B (N=xxx) n (%)	Total (N=xxx) n (%)
SUBJECTS WITH AT LEAST ONE MINOR PROTOCOL VIOLATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
CATEGORY 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEVIATION 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEVIATION 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
CATEGORY 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEVIATION 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEVIATION 2	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Subjects could have more than one minor protocol deviation. Percentages are based on the number of
all randomized subjects within each treatment group
Source Data: Listing 16.2.2.2

Table 14.1.2.1
Demographics and Baseline Characteristics
All Randomised Analysis Set

	A (N=xxx)	B (N=xxx)	Total (N=xxx)
AGE (YEARS)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	XX (XX.X)	XX (XX.X)	XX (XX.X)
MEAN (SD) XX.X (XX.XX)	XX (XX.X)	XX (XX.X)	XX (XX.X)
MEDIAN XX.X	XX (XX.X)	XX (XX.X)	XX (XX.X)
MIN, MAX XX, XX	XX (XX.X)	XX (XX.X)	XX (XX.X)
	XX (XX.X)	XX (XX.X)	XX (XX.X)
AGE CATEGORIES (YEARS)	XX (XX.X)	XX (XX.X)	XX (XX.X)
n (%)[2]			
1 XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
2 XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
3 XX (XX.X	XX (XX.X)	XX (XX.X)	XX (XX.X)
4 XX (XX.X	XX (XX.X)	XX (XX.X)	XX (XX.X)
5 XX (XX.X	XX (XX.X)	XX (XX.X)	XX (XX.X)
	XX (XX.X)	XX (XX.X)	XX (XX.X)
SEX n (%) [2]	XX (XX.X)	XX (XX.X)	XX (XX.X)
MALE XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
FEMALE XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	XX (XX.X)	XX (XX.X)	XX (XX.X)
RACE n (%) [2]	XX (XX.X)	XX (XX.X)	XX (XX.X)
WHITE	XX (XX.X)	XX (XX.X)	XX (XX.X)
ASIAN XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
BLACK XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
OTHER XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Table 14.1.2.1
Demographics and Baseline Characteristics
All Randomised Analysis Set

	A (N=xxx)	B (N=xxx)	Total (N=xxx)
HEIGHT (cm)			
n	xxx	xxx	xxx
MEAN (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
MEDIAN	xxx.x	xxx.x	xxx.x
MIN, MAX	xxx xxx	xxx xxx	xxx xxx
WEIGHT (KG)			
n	xxx	xxx	xxx
MEAN (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
MEDIAN	xxx.x	xxx.x	xxx.x
MIN, MAX XX, XX	xxx xxx	xxx xxx	xxx xxx
BODY MASS INDEX (BMI) (kg/m2))			
n	xxx	xxx	xxx
MEAN (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
MEDIAN	xxx.x	xxx.x	xxx.x
MIN, MAX XX, XX	xxx xxx	xxx xxx	xxx xxx

BMI=(body weight in kilograms)/(height in metres)**2.
Source Data: Listing 16.2.3.1

Table 14.1.3.1
Patient not requiring rescue anesthesia during surgery
All Randomized Analysis Set

	A (N=xxx) n (%)	B (N=xxx) n (%)	Total (N=xxx) n (%)
All patient randomized			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)
1			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)
2			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)
3			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)
4			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)
5			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 14.1.4.1
Patient not requiring rescue anesthesia during the two surgical procedures
All Randomized Analysis Set

	A (N=xxx) n (%)	B (N=xxx) n (%)	Total (N=xxx) n (%)
All patient randomized			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)
Calcaneo Stop			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)
Inguinal hernia repair			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)