# CLINICAL STUDY PROTOCOL

## Study CRO-17-133 - Sponsor code PAR.3-01-2017

## Dose-finding study of intrathecal paracetamol administered immediately before spinal anaesthesia with chloroprocaine HCl 1% for elective knee procedures of short duration

*Phase II, single centre, randomised, parallel-group, double-blind, three doses, placebo-controlled, exploratory efficacy and safety study*

| | |
|---|---|
| Test product: | Paracetamol 3%, solution for injection, Sintetica S.A., Switzerland |
| Control: | Placebo, 0.9% saline solution, Sintetica S.A., Switzerland |
| Sponsor: | Sintetica S.A., via Penate 5, CH-6850 Mendrisio, Switzerland<br>Phone: +41.91.640.42.50<br>Fax: +41.91.646.85.61 |
| Investigator: | Claudio Camponovo, MD. Chairman of the Department of Anaesthesiology, Clinica Ars Medica,<br>Via Cantonale, CH-6929 Gravesano, Switzerland<br>Email: ccamponovo@arsmedica.ch |
| Development phase: | Phase II |
| Version and date: | Final version 1.0, 16OCT17 |

*This study will be conducted in accordance with Good Clinical Practice (GCP), ICH topic E6 (R2)*



This document comprises 70 pages

## PROTOCOL APPROVAL

**SPONSOR**
Sintetica S.A., Switzerland

**Clinical Project Leader**
Elisabetta Donati, Corporate Director Scientific Affairs

16 OCT 2017 _____
Date

_____
Signature

**PRINCIPAL INVESTIGATOR**

*I have read this protocol and agree to conduct this study in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki, the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), and the applicable local law requirement, including supervising any individual or party to whom I will delegate trial-related duties and functions at the trial site.*

Claudio Camponovo, MD, Chairman
Department of Anaesthesiology, Clinica Ars Medica, Gravesano, Switzerland

16 - OCT - 2017 _____
Date Signature

**CRO**
CROSS Research S.A. and CROSS Metrics S.A., sister companies

**Coordination**
Emanuela Terragni, Clinical Project Leader

16 Oct 2017 — Date
Emanuela Terragni — Signature

**Medical Writing Representative**
Chiara Leuratti, Clinical Projects Unit Head

16 OCT 2017 — Date
Chiara Leuratti — Signature

**Biometry Unit Representative**
Matteo Rossini, Biometry Manager, Unit Head

16 OCT 2017 — Date
Matteo Rossini — Signature

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

16 Oct 2017 — Date
Mario Corrado — Signature

# STUDY SYNOPSIS

**Title:** Dose-finding study of intrathecal paracetamol administered immediately before spinal anaesthesia with chloroprocaine HCl 1% for elective knee procedures of short duration

**Protocol number:** CRO-17-133 Sponsor code PAR.3-01-2017

**Clinical phase:** Phase II

**Study design:** Phase II, single centre, randomised, parallel-group, double-blind, three doses, placebo-controlled, exploratory efficacy and safety study

**Planned nr. of centres / countries:** One / Switzerland

**Investigator and centre:** *Principal investigator:* Claudio Camponovo MD. Chairman, Department of Anaesthesiology, Clinica Ars Medica, Via Cantonale, CH-6929 Gravesano, Switzerland

**Investigational products:** Paracetamol 3% (30 mg/mL), solution for injection, Sintetica S.A., Switzerland. Three ascending doses of the paracetamol solution, administered by intrathecal injection, will be investigated. A fourth treatment group will only receive a placebo solution. Study treatment will be as follows:

- D1: 30 mg Paracetamol 3% (1 mL)
- D2: 60 mg Paracetamol 3% (2 mL)
- D3: 90 mg Paracetamol 3% (3 mL)
- P: Placebo (0.9% saline solution) (1 mL, 2 mL and 3 mL)

***Other products (Non-investigational medicinal product, NIMP)***
Chloroprocaine HCl 1% (10 mg/mL), injectable solution, Sintetica S.A., Switzerland, will be administered by intrathecal injection to all patients according to the Summary of Product Characteristics indications. The anaesthetic will be administered immediately after intrathecal paracetamol or placebo administration (maximal interval between administrations: 2 min).

**Dose regimen:** Eligible patients undergoing elective short-duration knee procedures up to 40 min (i.e. ≤ 40 min) duration (e.g. diagnostic knee arthroscopy and meniscectomy not requiring the micro-fracture technique) will be randomised into 4 treatment groups (15 patients per group) to receive either one of the 3 single doses of paracetamol 3% (D1, D2, D3) or the placebo solution (P) by intrathecal injection (IT), according to the randomised, parallel-group design. Immediately after IMP IT administration, all patients will receive a single IT dose of Chloroprocaine HCl 1% according to the Summary of Product Characteristics indications. The time interval between paracetamol IT and chloroprocaine IT injections should not exceed 2 min. Administrations' times will be recorded.

**Objective:** The objective of this study is to investigate the efficacy and safety of a single intrathecal injection of paracetamol, administered at 3 doses to 3 active treatment groups, as compared to placebo, for post-operative analgesia in knee procedures up to 40 min duration performed under spinal anaesthesia.

**Study endpoints/variables:**

**Primary efficacy endpoints/variable:**

- Pain intensity at rest evaluated using a 0-100 mm VAS at baseline (within 30 min before NIMP IT injection, 0 h), 1, 1.25, 1.5, 1.75, 2 h after NIMP IT injection, then every 30 min (i.e. 2.5, 3 h, etc.) after NIMP IT injection until eligibility for home discharge. Punctual VAS scores at the pre-specified time-points will be compared between treatments

**Secondary efficacy endpoints/variables:**

- Pain at rest VAS scores $AUC_{t1\text{-}t2}$, where $AUC_{t1\text{-}t2}$ is defined as the area under the pain intensity curve at the specified time-intervals (intervals: 0-2h, 0-4h)
- Pain at rest VAS scores $AUC_{last}$, where $AUC_{last}$ is defined as the area under the pain intensity curve from 0 h up to the last assessment time
- Time to first postoperative analgesia (level 1 or 2) ($T_{pa}$)
- Time to level 1 analgesia ($T_{A1}$)
- Time to level 2 analgesia ($T_{A2}$)
- Total amount of analgesic 1 consumption ($A_1$)
- Total amount of analgesic 2 consumption ($A_2$)
- Proportion of patients requiring analgesia (level 1 or level 2) in the first 2 h after surgery end ($\pi_{2h}$)
- Proportion of patients requiring analgesia (level 1 or level 2) in the first 4 h after surgery end ($\pi_{4h}$)
- Proportion of patients requiring analgesia (level 1 or level 2) from surgery end until eligibility for home discharge ($\pi_{ed}$)
- Proportion of patients requiring level 1 analgesia ($\pi_{A1}$) from surgery end until eligibility for home discharge

## STUDY SYNOPSIS (cont.)

**Study endpoints/variables, continued:**

**Secondary efficacy endpoints/variables, continued:**

- Proportion of patients requiring level 2 analgesia ($\pi_{A2}$) from surgery end until eligibility for home discharge
- Time to first supplementary analgesia, other than the planned level 1 or 2 analgesia ($T_{ao}$)
- Proportion of patients requiring supplementary analgesia, other than the planned level 1 or 2 analgesia ($\pi_{ao}$)
- Time to rescue anaesthesia ($T_{ras}$)
- Proportion of patients requiring rescue anaesthesia ($\pi_{ras}$)
- Time to onset of spinal block (i.e. time to readiness for surgery) ($T_{rs}$)
- Maximum level of sensory block ($SB_{max}$)
- Time to maximum level of sensory block ($T_{SBmax}$)
- Time to regression of spinal block ($T_{reg}$) (defined as complete regression of sensory block to S1)
- Time to unassisted ambulation ($T_{ua}$)
- Time to first spontaneous urine voiding ($T_{uv}$)
- Time to eligibility for home discharge ($T_{ed}$)

**Safety endpoints/variables**

- Treatment-emergent adverse events throughout the study
- Incidence of neurological complications including transient neurologic symptoms (TNS) at 24 h post-dose and at day 7±1
- Vital signs (blood pressure, heart rate), peripheral oxygen saturation ($SpO_2$)
- Concomitant medications

**Additional safety assessments**

- ECG at screening for patients > 60 years old
- ECG monitoring

**Sample size:** At least sixty (60) male/female patients (at least 15 patients per dose group), aged 18-80 years, scheduled for elective knee procedures up to 40 min duration (e.g. diagnostic knee arthroscopy and meniscectomy not requiring the micro-fracture technique) under spinal anaesthesia will be enrolled in order to have at least 15 treated patients per treatment group included in the Per Protocol Set. The sample size for the study is not based on any formal sample size calculation. The number of at least 15 treated patients/treatment group included in the Per Protocol Set is deemed appropriate considering the exploratory and descriptive nature of the study.

**Main selection criteria:**

**Inclusion criteria:**

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex, age and surgery*: male/female patients, 18-80 years old (inclusive), scheduled for short duration (up to 40 min) knee procedures
3. *Body Mass Index (BMI)*: 18 - 32 kg/m$^2$ inclusive
4. *ASA physical status*: I-III
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study.

**Exclusion criteria:**

1. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study. Contraindications to spinal anaesthesia. History of neuromuscular diseases to the lower extremities
2. *ASA physical status*: IV-V
3. *Further anaesthesia*: patients expected to require further anaesthesia
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principles (paracetamol and/or ester type anaesthetics) and/or formulations' ingredients or related drugs, non-steroidal anti-inflammatory drugs and/or opioid derivatives; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers could affect the outcome of the study
5. *Chronic pain syndromes*: patients with chronic pain syndromes taking opioids, anticonvulsant agents or chronic analgesic therapy
6. *Pain assessment*: patients anticipated to be unable to make a reliable self-report of pain intensity

## STUDY SYNOPSIS (cont.)

**Main selection criteria, continued:**
**Exclusion criteria, continued:**

7. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; ascertained psychiatric and neurological diseases, sepsis, blood coagulation disorders, severe cardiopulmonary disease, thyroid disease, diabetes, other neuropathies, history or evidence of heart failure. History of severe head trauma that required hospitalisation, intracranial surgery or stroke within the previous 30 days, or any history of intracerebral arteriovenous malformation, cerebral aneurism or CNS mass lesion
8. *Medications*: medication known to interfere with the extent of spinal blocks for 2 weeks before the start of the study. Paracetamol formulations, other than the investigational product, for 2 weeks before the start of the study and during the study. Hormonal contraceptives for females are allowed. Anti-hypotensive, anti-bradycardia (e.g. ephedrine, atropine, Ringer's solution), anti-haemetic and anti-nausea medications will be allowed
9. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
10. *Drug, alcohol*: history of drug or alcohol abuse according to the Investigator's opinion
11. *Pregnancy and lactation*: positive pregnancy test at screening (if applicable), pregnant or lactating women [*The pregnancy test will be performed to all fertile women and to all women up to 55 years old, if not in proven menopause (available laboratory test confirming menopause or surgically sterilised)]*

**Study schedule:**
The study will include a screening phase (Visit 1, Day -21/-1), a treatment phase (IMP IT administration, anaesthesia and surgical procedure: Visit 2, Day 1) and a follow-up phase including an observation period (Visit 3), a final visit and two follow-ups (24 h post-dose and day 7±1).

**Screening Phase (Visit 1, Day -21/-1):** Patients scheduled for short duration knee procedures (e.g. diagnostic knee arthroscopy and meniscectomy not requiring the micro-fracture technique) will be informed about the aims, procedures and possible risks of the study and will be asked to sign the informed consent form for the inclusion in the trial. Routine pre-surgery assessments will be performed according to the standard procedures of the hospital. A urine pregnancy test for women will be performed (if applicable according to the study inclusion/exclusion criteria). Inclusion/exclusion criteria will be verified and patients will be assigned a consecutive screening number. The following baseline characteristics will be recorded: demography, physical abnormalities, body weight, height, vital signs, peripheral oxygen saturation ($SpO_2$), medical/surgical history and previous/concomitant medications. Pain history will be recorded. ECG will be performed at screening for patients > 60 years old.

**Treatment Phase (Visit 2, Day 1):** Patients will be questioned about adverse events and concomitant medications and will be assigned a consecutive randomisation number. According to the randomisation list they will be allocated to receive one of three doses of paracetamol or one of the three volumes of the placebo solution. Blood pressure, heart rate, $SpO_2$ and ECG will be monitored using standard monitors at baseline and during block placement (see below) until at least the end of anaesthesia or longer, if necessary, according to the standard hospital procedures. Pain intensity will be measured at baseline using a 100 mm VAS. An antibiotic will be administered, if necessary, according to the standard hospital procedures. Before surgery, patients will be pre-medicated with propofol (1-2 mg/kg/h), if needed. In addition, if needed, Ringer's solution will be infused from the beginning until the end of surgery.
One of the three doses of paracetamol, depending on the treatment group, or placebo will be administered intrathecally (IT) just before spinal anaesthesia. After intrathecal administration of the paracetamol dose or placebo, the anaesthetic (Chloroprocaine HCl 1%) will be administered, as described in "Dose regimen" above. Time interval between the 2 administrations should not exceed 2 min. The time of paracetamol/placebo IT administration and the time of chloroprocaine IT administration will be recorded in the CRF. For the intrathecal injection of the paracetamol/placebo followed by the intrathecal injection of the anaesthetic, two needles will be used: one introducer needle, which will serve to introduce the second needle through the skin, plus one intrathecal Pencil point needle (27-G or 25-G Reganesth or Nizell needle) to which the first syringe containing paracetamol/placebo will be attached first, followed by the second syringe with the anaesthetic. In this way only one intrathecal puncture will be performed. Lumbar puncture will be done according to the standard hospital procedures.

## STUDY SYNOPSIS (cont.)

**Study schedule, continued:**
As also written above, during the spinal block hemodynamic variables (heart rate, blood pressure, $SpO_2$; ECG) will be monitored every 10 min until at least the end of anaesthesia, or longer if necessary, according to the standard hospital procedures. The time of start and the time of end of surgery will be recorded in the CRF.

**Follow-up Phase - Observation period (Visit 3: from Day 1 after surgery until final visit/ETV):**
Postoperatively, patients will be administered an analgesic as needed (see VAS scores below). Post-operative analgesia could include Ketorolac i.v. [Toradol] 30 mg (level 1 analgesia) and/or Tramadol i.v. 1 mg/kg (level 2 analgesia). The administered analgesic (level 1 or 2), the dose and intake frequency will be decided according to the reported surgery-related pain intensity (see below). Time of analgesic administration and details on the administered analgesic (name, dose, frequency) will be recorded in the CRF.

*Rescue analgesia/anaesthesia*
In case of incomplete anaesthesia during surgery or incomplete analgesia during surgery or postoperatively, either sedative, analgesics or anaesthetics will be administered according to the standard hospital's procedures. Details will be recorded in the CRF.

*Efficacy and safety assessments*
Pain intensity will be recorded for all patients using a 0-100 mm VAS at pre-specified time points, i.e. baseline (within 30 min before NIMP IT injection, 0 h), 1, 1.25, 1.5, 1.75, 2 h after NIMP IT injection, then every 30 min (i.e. 2.5, 3 h, etc.) after NIMP IT injection until eligibility for home discharge. Additional pain assessments could be performed if the patient spontaneously report surgery-related pain outside the pre-specified time-points. Also in this case, the patient will report pain intensity on the 0-100 mm VAS scale. If the score on the VAS scale is ≥ 4 at the pre-specified or additional assessment times, an analgesic will be administered as detailed above, according to the investigator's opinion.
Evolution of sensory and motor blocks will be evaluated by a blinded observer.

Treatment-emergent adverse events will be recorded and treated according to the standard procedures of the hospital. Particular attention will be given to systemic and local toxicity symptoms, neurological symptoms, including TNS, and allergic reactions. The occurrence of headache and lower limbs and gluteus paraesthesia, as well as nausea and vomiting will be carefully checked.

All primary, secondary study variables and additional assessments outcomes will be recorded in the CRF.

**Follow-up Phase - Final visit/ETV:** Patients will be eligible for home discharge when the criteria for discharge are met according to the standard hospital procedures. Patients will be actually discharged according to the hospitals' standard procedures. Before discharge patients will undergo a final visit (or early termination visit [ETV] in case of premature discontinuation from the study). Surgery-related pain intensity will be evaluated using a 0-100 mm VAS, vital signs and $SpO_2$ will be checked. Day and time of eligibility for home discharge and of actual discharge from the hospital will be recorded.

**Follow-up Phase - Follow-up:** At 24 h (Day 2) and on Day 7±1 (i.e. 6±1 days after analgesic/anaesthetic IT injection and surgery), the investigator or his deputy will question patients about symptoms of neurological complications including TNS and unusual sensations not associated with the operation area (buttock, thigh posterior, thigh anterior, lower limb, sacrum, calves, other areas) following prepared questions. Pain intensity at the injection site and surgery-related pain will also be assessed. Patients will be contacted by telephone if they have already left the hospital.

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

***Definition of analysis sets:***
*Enrolled Set*: all enrolled subjects. This analysis set will be used for demographic and baseline characteristics.
*Full Analysis Set (FAS)*: all randomised patients who fulfil the study protocol requirements in terms of investigational product (i.e. paracetamol/placebo) administration and anaesthetic administration and have at least one post-baseline assessment of the primary efficacy evaluation (i.e. surgery-related pain at rest). This analysis set will be used for the sensitivity analysis and for the secondary efficacy analysis.
*Per Protocol Set (PP)*: all randomised patients who fulfil the study protocol requirements in terms of investigational product administration, anaesthetic administration and primary efficacy evaluation (i.e. surgery-related pain at rest), with no major deviations that could affect the primary efficacy results. This analysis set will be used for the primary efficacy analysis and for the secondary efficacy analysis.

## STUDY SYNOPSIS (cont.)

**Data analysis, continued:**

***Definition of analysis sets, continued:***

*Safety Set*: all patients who receive at least one dose of the investigational product and/or anaesthetic. This analysis set will be used for the safety analyses.

***Efficacy analysis***

All study data will be listed by patient, treatment group and assessment time point/interval (if applicable) and will be summarised by treatment group and assessment time point/interval (if applicable) using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max) for quantitative variables and frequencies for qualitative variables. Summary statistics will be performed on the Per Protocol Set and on the Full Analysis Set.

***Primary efficacy analysis***

The primary efficacy analysis will be performed on the Per Protocol Set.
Pain at rest (VAS scores at each pre-defined time point) will be analysed using rank-transformed repeated measures ANCOVA with rank-transformed baseline pain at rest as covariate, and treatment, assessment time point and treatment*assessment time point as fixed effect. Pairwise comparisons between treatment groups for pain at rest will be performed at a two-sided type I error $\alpha = 0.05$ according to the following hierarchical order:

1. P vs. D3 (90 mg)
2. P vs. D2 (60 mg)
3. P vs. D1 (30 mg)
4. D1 (30 mg) vs. D3 (90 mg)
5. D2 (60 mg) vs. D3 (90 mg)
6. D1 (30 mg) vs. D2 (60 mg)

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

***Sensitivity analysis***

The primary efficacy analysis will be repeated on the Full Analysis Set. The same pairwise comparisons foreseen for the primary variable will be performed at a two-sided type I error $\alpha = 0.05$ according to the same hierarchical order.

***Secondary efficacy analysis***

Due to the small sample size, collected data will be compared using nonparametric tests.
$T_{pa}$, $T_{A1}$, $T_{A2}$, $T_{ao}$, $T_{ras}$, $T_{rs}$, $T_{SBmax}$, $T_{reg}$, $T_{ua}$, $T_{uv}$ and $T_{ed}$ will be presented using Kaplan-Meier curves and will be compared between treatment groups by log rank test.
$A_1$, $A_2$, $AUC_{t1\text{-}t2}$ ($AUC_{0\text{-}2h}$, $AUC_{0\text{-}4h}$) and $AUC_{last}$ will be summarised by treatment group using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max). $SB_{max}$, $\pi_{2h}$, $\pi_{4h}$, $\pi_{ed}$, $\pi_{A1}$, $\pi_{A2}$, $\pi_{ao}$ and $\pi_{ras}$ will be summarised by treatment group using frequency tables.
$SB_{max}$, $A_1$ and $A_2$ will be compared between treatment groups by Wilcoxon rank sum test.
$\pi_{2h}$, $\pi_{4h}$, $\pi_{ed}$, $\pi_{A1}$, $\pi_{A2}$, $\pi_{ao}$ and $\pi_{ras}$ will be compared between treatment groups using the Fisher exact test.
VAS scores for pain at rest $AUC_{t1\text{-}t2}$ ($AUC_{0\text{-}2h}$, $AUC_{0\text{-}4h}$) and $AUC_{last}$ will be analysed by rank-transformed ANOVA with treatment as fixed effect and by ANOVA with treatment as fixed effect.

***Safety analysis***

All study data will be listed by patient and treatment group and will be summarised by treatment group using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max) for quantitative variables and frequency for qualitative variables.

## STUDY SCHEDULE

| Visit | Visit 1 Day -21/-1 | Visit 2 Day 1 | Follow-up phase | | |
|---|---|---|---|---|---|
| | | | Visit 3 Observation period* | Final visit/ETV[9] | 24 h, Day 2 *and* Day 7±1 |
| **Informed consent** | x | | | | |
| **Demography** | x | | | | |
| **Medical/surgical history** | x | | | | |
| **Physical examination** | x | | | | |
| **Previous and concomitant medication** | x | x | x | x | x |
| **Height, Body mass index** | x | | | | |
| **Body weight** | x | | | | |
| **Vital signs (blood pressure, heart rate)[1]** | x | x | x | x | |
| **$SpO_2$[1]** | x | x | x | x | |
| **ECG[2]** | x[2] | x | x | | |
| **Pregnancy test (urine)[3]** | x | | | | |
| **Inclusion/exclusion criteria** | x | x | | | |
| **Eligibility evaluation** | x | x | | | |
| **Enrolment and Randomisation** | | x | | | |
| **Antibiotic, if needed, according to the standard hospital procedures** | | x | | | |
| **Propofol medication before surgery, if needed** | | x | | | |
| **Ringer's solution infusion, if needed** | | x | | | |
| **Paracetamol/Placebo IT administration** | | x | | | |
| **Chloroprocaine IT administration** | | x | | | |
| **Pain intensity (VAS)** | | x[4] | x[4] | x[5] | x[6] |
| **Blocks assessment[7]** | | x | x | | |
| **Surgery (< 40 min)** | | x | | | |
| **Post-operative analgesia[8]** | | | x | | |
| **Neurological complications (including TNS) questionnaire** | | | | | x |
| **Adverse events monitoring** | x | x | x | x | x |
| **Home discharge[9]** | | | | x | x |

**Observation period from the end of surgery to final visit/ETV. During the observation period, efficacy assessments and safety monitoring will be performed according to the protocol and standard safety monitoring procedures of the hospital.*

1. *Vital signs and $SpO_2$ at screening, at baseline (before the spinal injection), then every 10 min from spinal injection until at least the end of anaesthesia, or longer if necessary, according to the standard hospital procedures and before discharge (at final visit/ETV)*
2. *ECG at screening only for patients > 60 years old. ECG monitoring starting at baseline (before the spinal injection), then every 10 min from spinal injection until at least the end of anaesthesia, or longer if necessary, according to the standard hospital procedures*
3. *Pregnancy test performed according to the inclusion/exclusion criteria*

4. *Pain intensity at rest will be recorded using a 0-100 mm VAS at baseline (within 30 min before NIMP IT injection, 0h), 1, 1.25, 1.5, 1.75, 2 h after NIMP IT injection, then every 30 min (i.e. 2.5, 3 h, etc.) after NIMP IT injection until eligibility for home discharge*
5. *Pain intensity will be recorded before discharge (at final visit/ETV) using a 0-100 mm VAS*
6. *Surgery-related pain and pain at the injection site will be evaluated at the 24 h (Day 2) and Day 7±1 follow-ups (questionnaire)*
7. *The evolution of both sensory and motor blocks, including sensory block metameric level, will be evaluated every 5 min until readiness for surgery, then every 10 min until the maximum level is reached (two consecutive observations with the same level of sensory block only if applicable or if possible, otherwise one observation) and then every 15 min until complete regression of sensory block to S1*
8. *Patients will be administered an analgesic as needed. Post-operative analgesia will include Ketorolac i.v. [Toradol] 30 mg (level 1 analgesia) and/or Tramadol i.v. 1 mg/kg (level 2 analgesia)*
9. *Patients will be eligible for home discharge after the hospital criteria for discharge are met. Patients, however, will be discharged according to the hospital's standard procedures. In case of discontinuation, subjects will undergo an early termination visit (ETV)*

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## FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| γ-GT | γ-Glutamyl transpeptidase |
| β-HCG | human chorionic gonadotropin β |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALT | Alanine aminotransferase |
| ANOVA | Analysis of Variance |
| AST | Aspartate aminotransferase |
| $AUC_{t1-t2}$ | Area under the curve (AUC) over the interval from T1 to T2 |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CA | Competent Authority |
| CDISC | Clinical Data Interchange Standards Consortium |
| CSF | Cerebrospinal Fluid |
| CI | Confidence Interval |
| CMS | Clinical Medical Service |
| CNS | Central Nervous System |
| CPL | Clinical Project Leader |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CSP | Clinical Study Protocol |
| CRS | Clinical Study Report |
| CS | Clinically Significant |
| CV | Coefficient of Variation |
| D1 | 30 mg Paracetamol 3% (1 mL) |
| D2 | 60 mg Paracetamol 3% (2 mL) |
| D3 | 90 mg Paracetamol 3% (3 mL) |
| DBP | Diastolic Blood Pressure |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ETV | Early Termination Visit |
| FDA | Food and Drug Administration |
| FSFV | First Subject First Visit |
| GCP | Good Clinical Practice |
| GI | Gastro-intestinal |
| GLP | Good Laboratory Practice |
| HBs Ag | Hepatitis B virus surface antigen |
| HCV Ab | Hepatitis C virus antibodies |
| HIV | Human Immunodeficiency Virus |
| HR | Heart Rate |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IRB/IEC | Institutional Review Board/Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IT | intrathecal |
| IUD | Intra-Uterine Device |
| i.v. | Intravenous |
| LSLV | Last Subject Last Visit |
| MCH | Mean Cell Haemoglobin |
| MCHC | Mean Cell Haemoglobin Concentration |
| MCV | Mean Cell Volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRT | Mean Residence Time |
| MW | Molecular Weight |
| N | Normal |

| | |
|---|---|
| NA | Not Applicable |
| NCS | Not clinically significant |
| NIMP | Non Investigational Medicinal Product |
| NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| OTC | Over The Counter |
| P | Placebo solution (0.9% saline solution) |
| PDPH | Post-Dural-Puncture Headache |
| PT | Preferred Term |
| PTAE | Pre-Treatment Adverse Event |
| RASS | Richmond Agitation Sedation Scale |
| RBC | Red Blood Cells |
| SAE | Serious Adverse Event |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| $SpO_2$ | Peripheral oxygen saturation |
| SDTM | Study Data Tabulation Model |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | Treatment-Emergent Adverse Event |
| THC | delta-9-tetrahydrocannabinol |
| TNS | Transient Neurological Symptoms |
| USDA | United States Department of Agriculture |
| VAS | Visual Analogue Scale |
| WBC | White Blood Cells |
| WHODDE | World Health Organisation Drug Dictionary Enhanced |

# 1 INTRODUCTION

## 1.1 Background

### *1.1.1 Paracetamol*

Paracetamol (acetyl-p-aminophenol; Figure 1.1.1.1), also commonly known as acetaminophen in USA, is an active ingredient possessing analgesic and antipyretic activity, widely used in the medical practice to alleviate acute and chronic pain and to reduce the body temperature when this exceeds physiological values (1).

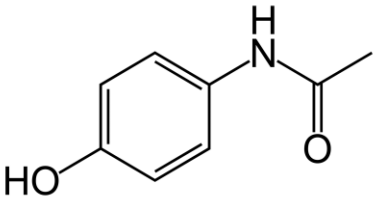


**Figure 1.1.1.1 Paracetamol molecular structure**

Paracetamol is almost devoid of antiaggregant and anti-inflammatory activity. To date, its mechanism of action remains little known, although the molecule was synthesised for the first time in 1878 and its use in the medical field has been established for more than 100 years (2).

In the clinical field, paracetamol is used as analgesic in the treatment of mild and medium pain (3) and as an antipyretic in the treatment of febrile states in adults and in children (2).
The most common pharmaceutical form for this active ingredient is the solid form. The most typical paracetamol-based pharmaceutical formulations are those in solid tablet form, in granule form or in the form of suppositories (4).
Formulations containing paracetamol in the form of a solution for intravenous (i.v.) infusion are also present on the market (5, 6, 7, 8). These are formulations indicated for the short-term treatment of pain of medium intensity, in particular of the type experienced following a surgical intervention. Intravenous (i.v.) administration is reserved for cases in which, from a clinical viewpoint, there is the need to treat the pain and/or hyperthermia with urgency or in cases in which it is impossible to implement the other administration methods.

Paracetamol can be effective even against severe pain if i.v. administered. In a repeated-dose, randomized, double-blind, placebo-controlled, 3-parallel group study in orthopaedic surgery patients comparing 1000 mg i.v. paracetamol (given at 6-h intervals over 24 h) and placebo, pain intensity, pain relief and rescue i.v. patient-controlled morphine use (time to use and amount used) were significantly decreased in the paracetamol group compared with the placebo group (9).

### *1.1.2 Spinal anesthesia*

Since paracetamol is devoid of anaesthetic action, it has never been used in the field of general, local or loco-regional anaesthesia, such as spinal anaesthesia. Spinal anaesthesia is an anaesthesia technique in which an injectable solution containing an active ingredient

possessing local anaesthetic activity is injected through the *dura mater*, i.e. the outer meningeal membrane protecting the spinal cord, into the medullary canal. The spinal injection is usually carried out by highly qualified medical personnel between the spinous processes of two vertebrae, usually in the lumbar zone, using specific needles, which are long and slender (10).
During the spinal injection, the risks of causing neurological damage are limited by the fact that the spinal column is protected by the *pia mater*, the innermost of the meningeal membranes.
During the infusion process, the solution containing the local anaesthetic mixes with the cerebrospinal fluid, thus blocking impulse conduction via the nervous system to the brain and causing a reversible loss of sensitivity, which may be accompanied by motor paralysis. Generally, spinal anaesthesia is used for interventions on organs of the small pelvis and on the lower limbs. Typical examples where spinal anaesthesia is used are appendectomy, hernioplasty, caesarean section, arthroscopy, orthopaedic surgery of the lower limbs, etc.

Among the spinal anaesthesia techniques, it is possible to distinguish between epidural injection and intrathecal (IT) injection. In the latter case, the solution containing local anaesthetic is injected into the subarachnoid space.

Whereas the intrathecal technique is more invasive than the epidural technique since the injection is performed in a deeper zone of the spine, it has the advantage of requiring comparably lower doses of local anaesthetic.

Depending on the local anaesthetic used, the spinal anaesthesia can last from one to three hours approximately. Once this action ceases, the patient progressively regains mobility and sensitivity and the perception of pain increases as time passes due to the effects of the surgical procedure. The analgesic action of local anaesthetics therefore remains limited to the period of the surgical intervention, for which reason it is essential to establish suitable analgesic therapy in the immediate post-surgical period.

### *1.1.3 Paracetamol for post-operative pain*

Paracetamol is frequently used as an analgesic in postoperative pain, alone or in combination with NSAIDs or opioids. Clinical pharmacology, safety and analgesic efficacy of paracetamol are well established by various routes of administration. A Cochrane review on 51 studies for a total of 5762 patients (3277 treated with a single oral dose of paracetamol and 2425 with placebo) concluded that a single dose of oral paracetamol provides effective analgesia for about half of the patients with acute postoperative pain, for a period of about 4 – 6 hours, and is associated with few, mainly mild, adverse events (3). Several studies available in the published literature show the efficacy of paracetamol administered intravenously either as paracetamol or as its pro-drug, propacetamol (9, 11-15). Alternative paracetamol administration routes in postoperative pain management have recently started to be explored in humans.

### *1.1.4 Paracetamol solution for spinal administration*

Sintetica S.A. has recently developed and patented a supersaturated Paracetamol 3% injectable solution for spinal administration to be administered intrathecally alone or before loco-regional anaesthesia for the treatment of postsurgical pain (10).

In preclinical studies performed in mice and rats, the spinal administration of the novel supersaturated solution at the doses of 200-500 µg resulted in effective analgesia against carrageen-induced inflammatory pain and in post-surgical pain, for at least 24 h (10). Four studies conducted in a rat model of mechanical hyperalgesia showed that the analgesic effect of the Paracetamol solution increased with increasing dose: in particular, treatment with 200 and 300 µg Paracetamol resulted in a statistically significant decrease from baseline in nociceptive pain, starting at the first time-point (i.e. 2 h) up to 48 h after spinal injection. With 500 µg paracetamol, the effect was still present at 72 h post-dose (4, 16-19).
In the studies, the administration of IT Paracetamol with IT chloroprocaine resulted in a significant effect up to 48 h after spinal injection when paracetamol was injected before chloroprocaine. The effect was evident at all investigated doses. No response was present when chloroprocaine was injected before paracetamol. Interestingly, the analgesic action of paracetamol appeared to have an additive effect with respect to the anaesthesia produced by the local anaesthetic. A clinical study is presently being conducted in patients undergoing hip replacement surgery under spinal anaesthesia to investigate the safety and efficacy of the newly developed paracetamol solution intrathecally administered at the three doses of 60, 90 and 120 mg, before the intrathecal administration of the anaesthetic (20).

## 1.2 Rationale

Results of the preclinical studies described above indicate that the newly developed Paracetamol 3% solution administered by intrathecal injection just before spinal anaesthesia has an analgesic effect on postoperative pain, with a long-lasting action which is maintained after the effect of the anaesthetic has ended. Preclinical data showed that IT administration of paracetamol supersaturated (5%) aqueous solution to rats was not associated to any neurotoxic effect (21).

The present study is being conducted to investigate the effectiveness and the safety of the supersaturated aqueous solution of paracetamol (Paracetamol 3% Sintetica), administered at 3 different doses, in patients undergoing short duration (up to 40 min) knee procedures under spinal anaesthesia.

The present study will evaluate the efficacy of the treatment in reducing post-operative pain in comparison to placebo. Spinal anaesthesia will be performed according to the standard hospital procedures using Chloroprocaine hydrochloride (HCl) 1%, a short-acting local anaesthetic belonging to the amino-ester class (22, 23), which is characterized by a rapid onset of action and spinal anaesthesia average duration of 80-100 min, depending on the amount used (23). This anaesthetic was approved in 2012 in Europe and is presently on the market in several European Countries, at the recommended doses of 40 and 50 mg, for spinal anaesthesia in adults where the planned surgical procedure should not exceed 40 min (23).

Chloroprocaine HCl 1% Sintetica has been on the Swiss market since 2002 for local anaesthesia and peripheral nerve block (22).

The safety of three doses of the Paracetamol 3% solution administered by IT injection, i.e 60, 90 and 120 mg, are presently being investigated in a two-part study performed in patients undergoing hip replacement surgery under spinal anaesthesia (20). Preliminary results confirm the safety of the administered doses (24).
The 60 mg, 90 mg and 120 mg doses of intrathecal Paracetamol 3% investigated in the above mentioned study were derived by an evaluation of the doses found to be efficacious in the preclinical studies (i.e. 200 – 500 µg; rat body weight: 175-199 g) and are 8 – 17 times lower than the doses normally administered in humans by the oral or i.v. route for post-operative pain control.
In the present study, lower doses of the Paracetamol 3% solution, i.e. 30 mg, 60 mg and 90 mg, will be investigated considering that the surgical procedures (i.e. knee procedures up to 40 min duration) are shorter, less invasive and possibly associated to a lower post-operative pain than the hip replacement surgery investigated in the previous study.

### 1.3 Risks and benefits

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

The risks for the study patients are anticipated to be low, considering that systemic adverse reactions following appropriate use of intrathecal paracetamol and intrathecal chloroprocaine are unlikely, due to the small dose absorbed.
Systemic toxicity is rarely associated with spinal anaesthesia but might occur after accidental intravascular injection.

The following undesirable effects have been reported following the oral and i.v. use of paracetamol: blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol. Hypersensitivity, including skin rash, and pain at the i.v. injection site have also been reported.

The possible undesirable effects due to the use of Chloroprocaine HCl 1% are generally similar to the undesirable effects of other local anaesthetics for spinal anaesthesia from the ester group. The undesirable effects induced by the medicinal product are difficult to distinguish from the physiological effects of the nerve block (e.g. reduction in arterial pressure, bradycardia, temporary urine retention), from direct effects (e.g. spinal hematoma) or the indirect effects (e.g. meningitis) of the injection or from the effects due to the loss of cerebrospinal liquid (e.g. post-spinal headache). Common effects reported on Chloroprocaine HCl 1% SmPC (23) are hypotension, anxiety, restlessness, paresthesia, dizziness, vomiting.

The intrathecal injection is quite an invasive administration technique. However, the technique is well-established and routinely used in all hospital anaesthesiology settings and is undertaken by clinicians with the necessary knowledge and experience. Even if in the study two products will be administered by intrathecal injection, only one injection in the subarachnoid space will be performed. In fact an introducer needle will be used. The syringe of paracetamol will be attached to a second needle, the intrathecal needle, and the paracetamol

will be injected. Then the syringe of the anaesthetic will be attached to the same intrathecal needle and the anaesthetic injected, thus reducing the discomfort and risk for the patients.

# 2 STUDY OBJECTIVES

The objective of this study is to investigate the efficacy and safety of a single intrathecal injection of paracetamol, administered at 3 doses to 3 active treatment groups, as compared to placebo, for post-operative analgesia in knee procedures up to 40 min duration performed under spinal anaesthesia.

## 2.1 Primary endpoint

- Pain intensity at rest evaluated using a 0-100 mm VAS at baseline (within 30 min before NIMP IT injection, 0 h), 1, 1.25, 1.5, 1.75, 2 h after NIMP IT injection, then every 30 min (i.e. 2.5, 3 h, etc.) after NIMP IT injection until eligibility for home discharge. Punctual VAS scores at the pre-specified time-points will be compared between treatments.

## 2.2 Secondary endpoints

### *2.2.1 Secondary efficacy endpoints*

- Pain at rest VAS scores $AUC_{t1\text{-}t2}$, where $AUC_{t1\text{-}t2}$ is defined as the area under the pain intensity curve at the specified time-intervals (intervals: 0-2h, 0-4h)
- Pain at rest VAS scores $AUC_{last}$, where $AUC_{last}$ is defined as the area under the pain intensity curve from 0 h up to the last assessment time
- Time to first postoperative analgesia (level 1 or 2) ($T_{pa}$)
- Time to level 1 analgesia ($T_{A1}$)
- Time to level 2 analgesia ($T_{A2}$)
- Total amount of analgesic 1 consumption ($A_1$)
- Total amount of analgesic 2 consumption ($A_2$)
- Proportion of patients requiring analgesia (level 1 or level 2) in the first 2 h after surgery end ($\pi_{2h}$)
- Proportion of patients requiring analgesia (level 1 or level 2) in the first 4 h after surgery end ($\pi_{4h}$)
- Proportion of patients requiring analgesia (level 1 or level 2) from surgery end until eligibility for home discharge ($\pi_{ed}$)
- Proportion of patients requiring level 1 analgesia ($\pi_{A1}$) from surgery end until eligibility for home discharge
- Proportion of patients requiring level 2 analgesia ($\pi_{A2}$) from surgery end until eligibility for home discharge
- Time to first supplementary analgesia, other than the planned level 1 or 2 analgesia ($T_{ao}$)
- Proportion of patients requiring supplementary analgesia, other than the planned level 1 or 2 analgesia ($\pi_{ao}$)
- Time to rescue anaesthesia ($T_{ras}$)
- Proportion of patients requiring rescue anaesthesia ($\pi_{ras}$)
- Time to onset of spinal block (i.e. time to readiness for surgery) ($T_{rs}$)
- Maximum level of sensory block ($SB_{max}$)
- Time to maximum level of sensory block ($T_{SBmax}$)
- Time to regression of spinal block ($T_{reg}$) (defined as complete regression of sensory block to S1)
- Time to unassisted ambulation ($T_{ua}$)

- Time to first spontaneous urine voiding ($T_{uv}$)
- Time to eligibility for home discharge ($T_{ed}$)

### *2.2.2 Secondary safety end-points*

- Treatment-emergent adverse events throughout the study
- Incidence of neurological complications including transient neurologic symptoms (TNS) at 24 h post-dose and at day 7±1
- Vital signs (blood pressure, heart rate), peripheral oxygen saturation ($SpO_2$)
- Concomitant medications

# 3 CLINICAL SUPPLIES

## 3.1 Treatment

### *3.1.1 Description of products*

#### *3.1.1.1 Test product*

| | |
|---|---|
| TEST IMP | Paracetamol 3% solution (30 mg/mL) |
| Manufacturer and Supplier | Sintetica S.A., Switzerland |
| Pharmaceutical form | Solution for injection (5-mL ampoule, filled with 4 mL of solution) |
| Dose | D1: 1 mL corresponding to 30 mg paracetamol<br>D2: 2 mL corresponding to 60 mg paracetamol<br>D3: 3 mL corresponding to 90 mg paracetamol |
| Administration route | Intrathecal |

#### *3.1.1.2 Reference product*

| | |
|---|---|
| CONTROL (P) | Placebo, 0.9% saline solution |
| Manufacturer and Supplier | Sintetica S.A., Switzerland |
| Pharmaceutical form | Solution for injection (5-mL ampoule) |
| Dose | 1, 2 or 3 mL |
| Administration route | Intrathecal |

#### *3.1.1.3 NIMP (Non investigational medicinal product)*

| | |
|---|---|
| Product name | Chloroprocaine HCl 1% (10 mg/mL) |
| Manufacturer and Supplier | Sintetica S.A., Switzerland |
| Pharmaceutical form | Solution for injection (5-mL ampoule) |
| Dose | According to the Summary of Product Characteristics indications |
| Administration route | Intrathecal |

### *3.1.2 Dose regimen*

Eligible patients undergoing elective short-duration knee procedures up to 40 min duration (e.g. diagnostic knee arthroscopy and meniscectomy not requiring the micro-fracture technique) will be randomised into four treatment groups (15 patients/group) to receive either one of the three single doses of Paracetamol 3% (D1, D2 or D3) or placebo solution (P) by intrathecal injection (IT), according to the randomised, parallel-group design.

In detail:

- Patients in D1 group will receive a single dose of 1 mL Paracetamol 3% (corresponding to 30 mg paracetamol).
- Patients in D2 group will receive a single dose of 2 mL Paracetamol 3% (corresponding to 60 mg paracetamol).

- Patients in D3 group will receive a single dose of 3 mL Paracetamol 3% (corresponding to 90 mg paracetamol).
- Patients in P group will receive a single dose of the placebo solution, as follows: 5 patients will receive 1 mL, 5 patients will receive 2 mL and 5 patients will receive 3 mL.

Immediately after paracetamol or placebo IT administration, all patients will receive a single IT dose of Chloroprocaine HCl 1%, according to the SmPC indications. The time interval between paracetamol IT and chloroprocaine IT administrations should not exceed 2 min.
The doses are summarised in the following scheme:

**Table 3.1.2.1 Dose groups**

| Dose group | N of patients | | IMP | Dose | All patients (within 2 min from paracetamol/placebo IT) |
|---|---|---|---|---|---|
| D1 | 15 | | Paracetamol 3% IT | 30 mg (1 mL) | Chloroprocaine HCl 1% (according to SmPC) |
| D2 | 15 | | | 60 mg (2 mL) | |
| D3 | 15 | | | 90 mg (3 mL) | |
| P | 15 | 5 | Placebo IT | 1 mL | |
| | | 5 | | 2 mL | |
| | | 5 | | 3 mL | |

### *3.1.2.1 General remarks*

The investigational product Paracetamol 3% will be provided in 5-mL ampoules, filled with 4 mL of solution, the placebo will be provided in 5-mL ampoules and the non-investigational product Chloroprocaine HCl 1% will be provided in 5-mL ampoules. The volume corresponding to the dose of paracetamol or placebo solution and the volume of the anaesthetic will be taken from the corresponding ampoule using a graduated syringe. The residual amount of paracetamol/placebo will be collected from the ampoule using another graduated syringe, completely sealable, and retained for drug accountability together with the empty ampoule.

## *3.1.3 Route and method of administration*

An antibiotic will be administered, if necessary, according to the standard hospital procedures. Before surgery, patients will be pre-medicated with propofol (1-2 mg/kg/h), if needed. In addition, if needed, Ringer's solution will be infused from the beginning until the end of surgery.

Paracetamol or placebo will be administered intrathecally (IT) just before spinal anaesthesia. Syringes for injection will be prepared by a person not involved in any other study-related activity. Paracetamol or placebo individual ampoules (one ampoule per patient) will be opened just before the administration. Details on the procedure for the preparation of the paracetamol/placebo syringes and on the injection procedure will be given in the study manual.

After intrathecal administration of the paracetamol dose or placebo, the anaesthetic (Chloroprocaine HCl 1%) will be administered. Time interval between the 2 administrations

should not exceed 2 min. The time of paracetamol/placebo IT administration and the time of chloroprocaine IT administration will be recorded in the case report form (CRF).

The injections will be performed according to the hospital procedures. For the intrathecal injection of paracetamol/placebo followed by the intrathecal injection of the anaesthetic, two needles will be used: one introducer needle, which will serve to introduce the second needle through the skin, plus one intrathecal Pencil point needle (27-G or 25-Gauge or Reganesth or Nizell needle) to which the first syringe containing paracetamol will be attached first, followed by the second syringe with the anaesthetic. In this way only one intrathecal puncture will be performed. Lumbar puncture will be done according to the standard hospital procedures.

Postoperatively, patients will be administered an analgesic as needed (see § 7.3 and 7.4). Post-operative analgesia will include Ketorolac i.v. [Toradol] 30 mg (level 1 analgesia) and/or Tramadol i.v. 1 mg/kg (level 2 analgesia).
The administered analgesic (level 1 or 2), analgesic dose and intake frequency will be decided by the investigator according to the reported surgery-related pain intensity. Time of analgesic administration and details on the administered analgesic (name, dose, frequency) will be recorded on the CRF.

In case of incomplete anaesthesia during surgery or incomplete analgesia during surgery or postoperatively, either sedative, analgesics or anaesthetics will be administered according to the standard hospital's procedures. Details will be recorded in the CRF.

### *3.1.4 Investigational product distribution*

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

## 3.2 Packaging and labelling

Packaging and labelling of the investigational products (Paracetamol 3% and Placebo solution) will be carried out by the Sponsor. The primary packaging of the investigational products will be a 5-mL glass ampoule packed in individual carton packages (patients' kits).

Labelling in local language will report all the information requested according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in "The rules governing medicinal products in the European Community", Volume 4; 25).

Labelling on packages will report:

a) Name, address and telephone number of the sponsor and CRO;

b) Pharmaceutical dosage form, route of administration, quantity of dosage units, the name/identifier and strength/potency;

c) Batch number;

d) Study Nr.;

e) The study subject identification number/treatment number;
f) Expiry in month/year format and in a manner that avoids any ambiguity;
g) Investigator's name;
h) Directions for use;
i) "For clinical trial use only" wording;
j) The storage conditions.

Labels of the individual syringes of the investigational products (paracetamol/placebo) will report only the patient's randomisation number and the kit number.
Further details on the products packaging will be given in the study manual.

Packaging of the anaesthetic (Chloroprocaine HCl 1%) will be the commercial packaging.

### 3.3 Storage conditions

The investigational products (Paracetamol and Placebo) and the non-investigational product (Chloroprocaine HCl 1%) must be stored at 15-25°C. The products will be stored in a dry locked place, sheltered from light. The products will not be refrigerated or frozen.

### 3.4 Drug accountability

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

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

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

# 4 INVESTIGATIONAL PLAN

## 4.1 Overall study design

This is a phase II, single centre, randomised, parallel-group, double-blind, three doses, placebo-controlled, exploratory efficacy and safety study.

## 4.2 Discussion of design

This study has been designed to evaluate the effectiveness of a novel aqueous solution of Paracetamol (Paracetamol Sintetica 3%) administered by intrathecal injection before spinal anesthesia in patients undergoing elective short-duration knee procedures up to 40 min duration (e.g. diagnostic knee arthroscopy and meniscectomy not requiring the micro-fracture technique) under spinal anaesthesia. In particular the study will investigate the effectiveness of the three paracetamol doses, administered by intrathecal injection before spinal anaesthesia, in reducing postoperative pain.

Administration of paracetamol for postoperative pain management using methods alternative to the traditional oral or i.v. routes is being explored in humans. Results of preclinical studies conducted in rat models of mechanical hyperalgesia indicated that the newly developed Paracetamol 3% solution administered by intrathecal injection just before spinal anaesthesia has an analgesic effect on postoperative pain, with a long-lasting action which is maintained after the effect of the anaesthetic has ended.

The study will be placebo-controlled. Each patient will be allocated to a treatment arm (one of the three paracetamol doses or one of the three volumes of the placebo solution) according to a computer-generated randomisation list.

The doses of intrathecal Paracetamol 3% investigated in a previous study, i.e. 60, 90 and 120 (24), were derived by an evaluation of the doses found to be safe and efficacious in the preclinical studies (i.e. 200 – 500 µg; rat body weight: 175-199 g) and were 8 – 17 times lower than the doses normally administered in humans by the oral or i.v. route for post-operative pain control. These doses, intrathecally administered, have been shown to be safe in patients undergoing hip replacement surgery (24). In the present study, lower doses of the Paracetamol 3% solution, i.e. 30 mg, 60 mg and 90 mg, will be investigated considering that the surgical procedures (i.e. knee procedures up to 40 min duration) are shorter, less invasive and possibly associated to a lower post-operative pain than the hip replacement surgery investigated in the previous study.

Two products [1-Paracetamol (or placebo); 2-Anaesthetic] will be administered to each patient by intrathecal injection. However, only one injection in the subarachnoid space will be performed. For the procedure two needles, an introducer needle and a Pencil point intrathecal needle will be used. First, the syringe of paracetamol will be attached to the intrathecal needle and the paracetamol will be injected. Then the paracetamol syringe will be detached from the needle, the anaesthetic syringe will be attached to the same intrathecal needle and the anaesthetic injected, thus reducing the discomfort and risk for the patients.

The study will be double-blind. Neither the Investigator/co-investigators/study nurses involved in the clinical study procedures, nor will the patients be aware of the administered treatment. Syringes for injection will be prepared by a person not involved in any study-related activities where a bias is possible.

Spinal anaesthesia will be performed according to the standard hospital procedures using Chloroprocaine HCl 1%, a short-acting local anaesthetic characterized by a rapid onset of action and spinal anaesthesia average duration of 80-100 min, depending on the amount used (23).

In the present study the occurrence of neurological complications including TNS, which have been reported after spinal anaesthesia, will be carefully monitored. In addition, for all intrathecal injections a 27- or 25-Gauge Pencil point needle will be used in order to decrease the risk of Post-Dural-Puncture Headache (PDPH) occurrence.

Occurrence of clinically relevant hypotension and bradycardia) will be monitored throughout the study and if observed appropriately treated, according to the standard hospital procedures.

Pre-medication with propofol will be performed, if needed, to reduce possible anxiety before the operation. This is common clinical practice. Propofol at the indicated doses will not influence the patient pain perception.

# 5 STUDY POPULATION

## 5.1 Target population

Patients aged 18-80 years, scheduled for elective knee procedures up to 40 min duration (e.g. diagnostic knee arthroscopy and meniscectomy not requiring the micro-fracture technique) under spinal anaesthesia.

## 5.2 Inclusion criteria

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

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex, age and surgery*: male/female patients, 18-80 years old (inclusive), scheduled for short duration (up to 40 min) knee procedures
3. *Body Mass Index (BMI)*: 18 - 32 kg/m$^2$ inclusive
4. *ASA physical status*: I-III
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study.

## 5.3 Exclusion criteria

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

1. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study. Contraindications to spinal anaesthesia. History of neuromuscular diseases to the lower extremities
2. *ASA physical status*: IV-V
3. *Further anaesthesia*: patients expected to require further anaesthesia
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principles (paracetamol and/or ester type anaesthetics) and/or formulations' ingredients or related drugs, non-steroidal anti-inflammatory drugs and/or opioid derivatives; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers could affect the outcome of the study
5. *Chronic pain syndromes*: patients with chronic pain syndromes taking opioids, anticonvulsant agents or chronic analgesic therapy
6. *Pain assessment*: patients anticipated to be unable to make a reliable self-report of pain intensity
7. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; ascertained psychiatric and neurological diseases, sepsis, blood coagulation disorders, severe cardiopulmonary disease, thyroid disease, diabetes, other neuropathies, history or evidence of heart failure. History of severe head trauma that required

hospitalisation, intracranial surgery or stroke within the previous 30 days, or any history of intracerebral arteriovenous malformation, cerebral aneurism or CNS mass lesion

8. *Medications*: medication known to interfere with the extent of spinal blocks for 2 weeks before the start of the study. Paracetamol formulations, other than the investigational product, for 2 weeks before the start of the study and during the study. Hormonal contraceptives for females are allowed. Anti-hypotensive, anti-bradycardia (e.g. ephedrine, atropine, Ringer's solution), anti-haemetic and anti-nausea medications will be allowed
9. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
10. *Drug, alcohol*: history of drug or alcohol abuse according to the Investigator's opinion
11. *Pregnancy and lactation*: positive pregnancy test at screening (if applicable), pregnant or lactating women [*The pregnancy test will be performed to all fertile women and to all women up to 55 years old, if not in proven menopause (available laboratory test confirming menopause or surgically sterilised)]*

### *5.3.1 Not allowed treatments and other treatments*

No medication known to interfere with the extent of spinal block will be allowed for 2 weeks before the start of the study and during the whole study duration (except for medications administered as part of the study).
Paracetamol formulations, other than the investigational product, will not be allowed for 2 week before the start of the study and during the study.
Hormonal contraceptives for females are allowed.

Anti-hypotensive, anti-bradycardia (e.g. ephedrine, atropine, Ringer's solution), anti-haemetic and anti-nausea medications will be allowed.

The area to be operated will be aseptically prepared with iodine-based disinfectants, e.g. chlorhexidine.

An antibiotic will be administered, if needed, according to the standard hospital procedures. Before surgery, patients will be pre-medicated with propofol (1-2 mg/kg/h), if needed. In addition, if needed, Ringer's solution will be infused from the beginning to the end of surgery.

Postoperatively, patients will be administered an analgesic as needed (see § 7.3 and 7.4). Post-operative analgesia will include Ketorolac i.v. [Toradol] 30 mg (level 1 analgesia) and/or Tramadol i.v. 1 mg/kg (level 2 analgesia).

In case of incomplete anaesthesia during surgery or incomplete analgesia during surgery or postoperatively, either a sedative, analgesic or anaesthetic will be administered according to the standard hospital's procedures. Details will be recorded in the CRF.

# 6 STUDY SCHEDULE

The schedule of the study is summarised at page 10.

## 6.1 Study visits and procedures

The study will include a screening visit, one treatment phase, followed by a follow-up phase with an observation period, a final visit and two follow-ups. A written informed consent will be obtained before enrolment in the study.

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

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening - visit 1: between Day -21 and Day -1
- **Treatment phase**
  - Visit 2 - Day 1: paracetamol/placebo IT administration, anaesthesia and surgery
- **Follow-up phase**
  - Visit 3 (Observation period) – from Day 1 after surgery until final visit/ETV:
    - Efficacy and safety assessments
  - Final visit/early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV)
  - Follow-up at 24 h after analgesic and anaesthetic IT injection and surgery (Day 2)
  - Follow-up on Day 7±1 (i.e. 6±1 days after analgesic/anaesthetic IT injection and surgery)

Study visits and procedures are detailed below:

## Study schedule

| | Day | Procedures/Assessments | Notes |
|---|---|---|---|
| **Screening Phase Visit 1** | *From day -21 to day -1* | ➢ Explanation to the patient of study aims, procedures and possible risks<br>➢ Informed consent signature<br>➢ Screening number (as S001, S002, etc.)<br>➢ Demographic data<br>➢ Previous/concomitant medications<br>➢ Routine pre-surgery assessments according to the hospital standard procedures, including medical/surgical history, pain history, physical examination, height, weight, vital signs (blood pressure, heart rate), $SpO_2$<br>➢ ECG for patients > 60 years old<br>➢ Urine pregnancy test for women, if applicable<br>➢ Inclusion/exclusion criteria evaluation<br>➢ Eligibility evaluation<br>➢ AE monitoring | |
| **Treatment Phase Visit 2** | *Day 1* | ➢ Concomitant medications<br>➢ Adverse events<br>➢ Inclusion/exclusion criteria evaluation<br>➢ Eligibility evaluation<br>➢ Subject randomisation<br>➢ Vital signs, $SpO_2$ and ECG monitoring (if applicable) until at least the end of anaesthesia, or longer if necessary, according to the standard hospital procedures<br>➢ Baseline pain assessment at rest using a 0-100 mm visual analogue scale (VAS)<br>➢ Premedication:<br>• Antibiotic, if needed, according to the hospital practice<br>• Propofol (before surgery), if needed<br>• Ringer's solution (from surgery start to surgery end), if needed<br>➢ Paracetamol/placebo intrathecal injection<br>➢ Anaesthesic intrathecal injection<br>➢ Blocks assessment<br>➢ Surgery (up to 40 min duration) | |

| | Day | Procedures/Assessments | Notes |
|---|---|---|---|
| **Follow-up Phase Observation period – Visit 3** | *Day 1 after surgery until final visit/ETV* | ➢ Concomitant medications<br>➢ Adverse events<br>➢ Vital signs, $SpO_2$ and ECG monitoring (if applicable) until at least the end of anaesthesia, or longer if necessary, according to the standard hospital procedures<br>➢ Pain assessment at rest at 1, 1.25, 1.5, 1.75, 2 h after NIMP IT injection, then every 30 min (i.e. 2.5, 3 h, etc.) after NIMP IT injection until eligibility for home discharge using a 0-100 mm VAS<br>➢ Additional post-operative analgesia, only if needed<br>➢ Blocks assessment, if applicable | Standardised meals will be served according to the hospital procedures. |
| **Follow-up Phase Final Visit/ETV** | *At the end of the observation period or upon discontinuation for ETV* | ➢ Final assessments, including surgery-related pain assessment at rest (0-100 VAS), according to the hospital's standard procedures<br>➢ Vital signs (BP, HR), $SpO_2$<br>➢ Concomitant medications<br>➢ Adverse events<br><br>In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s) | Patients will be <u>eligible</u> for home discharge when criteria for discharge are met. Patients will be actually discharged from the hospital according to the standard hospital procedures |
| **Follow-up Phase Follow-ups** | *Day 2, 24 h post-dose* | ➢ Adverse events, including neurological complications and TNS (questionnaire)<br>➢ Pain at the injection site and surgery-related pain<br>➢ Concomitant medications | Follow-ups will be performed by telephone if the patient has left the hospital |
| | *Day 7±1* | ➢ Adverse events, including neurological complications and TNS (questionnaire)<br>➢ Pain at the injection site and surgery-related pain<br>➢ Concomitant medications | |

## 6.2 Diet and lifestyle

Study participants will follow the study procedures according to the decision of the study investigator. Patients will arrive at the clinical centre either in the morning of the scheduled surgery day or the previous evening, according to the hospital requirements, and will be discharged after meeting the hospital criteria for discharge (<u>eligibility</u> for home discharge) and according to the hospital procedures.

On Day 1, patients will be under fasting conditions before surgery. Clear fluids intake is allowed until 2 h before surgery. The patients will remain under fasting conditions according to the investigator's opinion. Meals will be served according to the hospital's standard procedures.

# 7 DESCRIPTION OF SPECIFIC PROCEDURES

## 7.1 Physical examination

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

Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs.

### *7.1.1 Vital signs and peripheral oxygen saturation ($SpO_2$)*

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

Vital signs (blood pressure, heart rate) and $SpO_2$ will be checked at screening and monitored starting at baseline (before the spinal injection) then every 10 min from spinal injection until at least the end of the anaesthesia, or longer if necessary, according to the standard hospital procedures. Standard monitors will be used according to ASA recommendations.

Blood pressure, heart rate and $SpO_2$ will be monitored also before discharge at final visit/ETV.

Monitoring after spinal injection will be performed for safety reasons and results will not be reported in the CRF, unless clinical significant values are observed. Screening, baseline and before discharge assessments of haemodynamic variables and any other assessment after the surgery judged clinical significant will be reported in the CRF.

Occurrence of clinically relevant hypotension and bradycardia will be monitored throughout the study and, if observed, appropriately treated, according to the Investigator's opinion.

### *7.1.2 ECGs*

ECG will be performed at screening for patients > 60 years old. ECG will be monitored in all patients using standard monitors at baseline (before the spinal injection), during the block (every 10 min) until at least the end of anaesthesia, or longer if necessary, according to the standard hospital procedures.

Monitoring will be performed for safety reasons. Results will be assessed by the Investigator/his deputies and not recorded in the CRF unless clinically significant.

## 7.2 Assessment of treatment-emergent adverse events

### *7.2.1 Treatment-emergent adverse events (TEAEs)*

For the definition of adverse events (AEs) and treatment-emergent adverse events (TEAEs) please refer to § 11.

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

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

Any complication during anaesthesia will be recorded (and treated according to the standard hospital procedures). Pain at the site of injection and any other pain not related to surgery will be recorded as adverse event.
Surgery-related pain at the site of surgery will not be recorded as an adverse event (see § 7.3, Pain intensity).

Particular attention will be given to systemic and local toxicity symptoms, neurological symptoms and allergic reactions. The occurrence of headache and of lower limbs and gluteus paraesthesia, as well as nausea and vomiting will be carefully checked. Patients will also be instructed to report any signs of systemic (central nervous system) toxicity.

### *7.2.2 Neurological complications and transient neurological symptoms*

Attention will be given to the possible occurrence of neurological complications including transient neurological symptoms (TNS). In particular the incidence of neurological complications including TNS and unusual sensations not associated to the operation area will be assessed at 24 h and at day 7±1 (i.e. 6±1 days) after analgesic/anaesthetic IT injection and surgery, directly or through a telephonic interview (if the patient has already left the hospital). A specific questionnaire will be filled-in and the following symptoms will be questioned (see Appendix 18.1):

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

Symptoms reported through the questionnaires will also be recorded as adverse events (see § 7.2.1).
The questionnaire will be reviewed by the investigator who will judge whether the reported symptoms could be classified as neurological complications or TNS (this information will be reported in the CRF) on the basis of the available evidence and referring to the diagnosis criteria reported by Pollock *et al.* (26) and ASA, and summarised in the table below:

**Table 7.2.2.1 Differential diagnosis criteria for neurological complications including TNS and other events following intrathecal injection**

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

## 7.3 Pain intensity at rest

Surgery-related pain intensity at rest will be assessed by the patients using a 0-100 mm visual analogue scale (VAS) at the following time-points:

- Baseline (within 30 min before NIMP IT injection, 0 h), 1, 1.25, 1.5, 1.75, 2 h after NIMP IT injection, then every 30 min (i.e. 2.5, 3 h, etc.) after NIMP IT injection until eligibility for home discharge.

Surgery-related pain intensity will also be assessed before discharge (at final visit/ETV) using a 0-100 mm VAS.

Additional pain assessments could be performed if the patient spontaneously report pain outside the pre-specified time-points. Also in this case, the patient will report surgery-related pain intensity on the 0-100 mm VAS scale.
If the score on the VAS scale is ≥ 4 at the pre-specified or additional assessment times, an analgesic will be administered as detailed in § 7.4.
VAS scores will be measured and reported in the CRF by the Investigator or his/her deputy.

The study primary efficacy measures will be the VAS scores at each predefined time-point after the NIMP IT injection until eligibility for home discharge whilst the additional assessments and the assessment before discharge will not be taken into account for the primary efficacy analysis.

VAS assessment times should not deviate more than the recommended tolerance ranges summarised in the following table.

**Table 7.3.1 Recommended tolerance ranges for the scheduled VAS assessment times**

| VAS assessment times | Tolerance ranges |
|---|---|
| Baseline (0 h) | Within 30 min before the IT injection |
| 1, 1.25, 1.5, 1.75, 2, 2.5 hours after NIMP injection | ± 5 min |
| 3 hours after NIMP injection and all other assessments until eligibility for home discharge | ± 10 min |
| Before discharge (at final visit/ETV) | Not applicable |

Any deviations from the scheduled VAS assessment times outside the tolerance ranges will be verified through Data Clarification Forms.

Pain at the injection site will be recorded independently of surgery-related pain and will be reported as AE. Surgery-related pain will not be reported as AE (see § 7.2.1).

Pain at the injection site will also be assessed at the two follow-ups (24 h post-dose and day 7±1) using a questionnaire (see § 7.2.2). The following grading system will be used for pain at the site of injection:

Scores 0, 1, 2 => No adverse event
Scores 3, 4, 5 => Adverse event with severity 'Mild'
Scores 6, 7, 8 => Adverse event with severity 'Moderate'
Scores 9, 10 => Adverse event with severity 'Severe'

## 7.4 Post-operative pain control

Postoperatively, patients will be administered an analgesic as needed (see § 7.3). Post-operative analgesia could include Ketorolac i.v. [Toradol] 30 mg (level 1 analgesia) and/or Tramadol i.v. 1 mg/kg (level 2 analgesia).

The administered analgesic (level 1 or 2), analgesic dose and intake frequency will be decided according to the reported surgery-related pain intensity.

Time of analgesic administration and details on the administered analgesic (name, dose, frequency) will be recorded on the CRF.

### 7.5 Rescue analgesia/anaesthesia

In case of incomplete anaesthesia during surgery or incomplete analgesia during surgery or postoperatively, either a sedative, analgesic or anaesthetic will be administered according to the standard hospital's procedures. Details will be recorded in the CRF.

### 7.6 Block assessment

The evolution of both sensory and motor blocks, including sensory block metameric level, will be evaluated every 5 min until readiness for surgery (see definition below), then every 10 min until the maximum level is reached (two consecutive observations with the same level of sensory block only if applicable or if possible, otherwise one observation) and then every 15 min until complete regression of sensory block to S1.

***Sensory block*** will be verified by bilateral Pinprick test using a 20-G hypodermic needle and will be recorded. Pinprick sensation will be scored as being present (score 1) or absent (score 0). Onset of sensory block is defined as an absent touch sensation (score 0).

***Motor block*** will be verified using a modified Bromage scale (0=no block; 1=hip blocked; 2=hip and knee blocked; 3=hip, knee and ankle blocked). Onset of motor block is defined as a motor block score $\geq 2$.

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

**Spinal block/Readiness for surgery** is defined as the presence of an adequate motor block (Bromage's score $\geq 2$) and loss of Pinprick sensation, according to the Investigator's opinion. Time to readiness for surgery is defined as the time from the spinal injection (time 0 h) to achievement of readiness for surgery.

Regression (offset) of sensory block will be deemed to have occurred when sensitive sensation has returned (score 1). Regression (offset) of motor block will be deemed to have occurred when motor score returns to 0.

Time of onset of spinal block (i.e. time to readiness for surgery), Maximum level of sensory block, Time of maximum level of sensory block and Time of regression of spinal block (defined as time to complete regression of sensory block to S1), will be reported in the CRF. Start time and end time of surgery will also be recorded.

## 7.7 Procedures for assessing eligibility for home discharge

Patients will stay in the hospital after surgery until at least they are considered eligible for home discharge.
Patients will be eligible for home discharge when the criteria for discharge are met, according to the standard hospital procedures (generally: autonomous ambulation, absence of surgical pain, ability to take food).

At final visit/ETV, patients will be asked about any adverse events, with particular attention to local toxicity and neurological symptoms, such as paraesthesia of the gluteus and of the lower limb, and to possible allergic reactions (e.g. urticarial). Pain will be assessed as specified in § 7.3. Vital signs and $SpO_2$ will be checked.
The patients will be actually discharged according to the hospital's standard procedures.

# 8 ASSIGNMENT OF STUDY TREATMENT

## 8.1 Randomisation

The randomisation list will be computer generated by the Biometry Unit of the Clinical Contract Research Organization (CRO), using the PLAN procedure of the SAS® system version 9.3 (TS1M1) (27) or higher for Windows (the version will be stated in the final clinical study report). The randomisation list will be attached to the final clinical study report.

## 8.2 Treatment allocation

The patients will be allocated to D1, D2, D3 or one of the P volumes according to the study randomisation list.

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

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

All patients will receive Chloroprocaine HCl 1% as spinal anaesthetic after intrathecal injection of the IMP and before the surgical procedure (see § 3.1.2).

## 8.3 Blinding

The study is double-blind, i.e. the Investigator and the patients will not be aware of the administered investigational product.

Three (3) copies of the list will be generated and sealed in individual envelopes:

- one copy will be sent to the manufacturer for the preparation of the individual treatment boxes
- one copy will be kept at the CRO Quality Assurance Unit
- one copy will be stored in the CROSS Metrics Project File

Neither the members of the clinical staff nor the CPL or the CRA/monitor, monitoring the study evaluations and procedures, will have access to the randomisation code.
Only the person preparing the syringe (and not involved in any other study-related procedure) and the CRA/monitor who performs the drug accountability will be aware of the administered investigational product.
The CRO will open the envelope containing the randomisation list only when data-entry is complete and decisions to be made in blinding, before data analysis, are final.

The CRO will notify breaking of the randomisation list to the sponsor.

Syringes for injection will be prepared by a person not involved in any study-related activities where a bias is possible.

### *8.3.1 Emergency code and unblinding procedures*

Unblinding of the code for specific patients, if applicable, will be fully documented in the source documents, in the CRFs and in the clinical study report.

### *8.3.2 Emergency individual envelopes*

The emergency envelopes containing the individual randomisation codes will be sent to the clinical centre.

The randomisation code will be filed in the investigator's study file in a sealed envelope for each patient, with the key for its identification. Copies of the individual emergency envelopes will be sent to the pharmacovigilance representative and to the sponsor representative (if not coinciding).

Inside each envelope, the individual randomisation code must be clearly indicated, reporting the allocated treatment.

Breaking of an individual randomisation code during the study is allowed only when knowledge of the code is essential for the patient's health. In this case, only the envelope related to the concerned subject will be opened. Individual code breaking will be clearly reported in the patient CRF and on the envelope; the latter is sealed again.

In any case, the monitor must be informed within 24 h from code breaking.

The date and the reason for breaking the code must be recorded in the CRF and on the envelope. All envelope sets containing the randomisation code of each patient must be kept closed even after database lock. At the end of the study, all envelope sets will be sent to the sponsor.

### *8.3.3 Individual kit replacement envelopes*

The clinical centre will also receive individual kit replacement envelopes. If a reserve kit needs to be used, the kit replacement envelope will be opened and the injectable solution will be prepared out of the operating room by a person not involved in any other study activity in such a way that the double-blind condition of the study is maintained. The date and the reason for opening the kit replacement envelope will be recorded on the envelope and then the envelope will be sealed again.

All kit replacement envelope sets must be kept closed even after database lock. At the end of the study, all envelope sets will be sent to the sponsor.

# 9 EVALUATION PARAMETERS

## 9.1 Study variables

### *9.1.1 Primary efficacy variables*

The primary efficacy variables will be the VAS scores at each predefined time-point.

Pain intensity at rest (as VAS scores) will be evaluated using a 0-100 mm VAS at baseline (within 30 min before NIMP IT injection, 0 h), 1, 1.25, 1.5, 1.75, 2 h after NIMP IT injection, then every 30 min (i.e. 2.5, 3 h, etc.) after NIMP IT injection until eligibility for home discharge.

### *9.1.2 Secondary efficacy variables*

- Pain at rest VAS scores $AUC_{t1\text{-}t2}$, where $AUC_{t1\text{-}t2}$ is defined as the area under the pain intensity curve at the specified time-intervals (intervals: 0-2h, 0-4h)
- Pain at rest VAS scores $AUC_{last}$, where $AUC_{last}$ is defined as the area under the pain intensity curve from 0 h up to the last assessment time
- Time to first postoperative analgesia (level 1 or 2, see below) ($T_{pa}$)
- Time to level 1 analgesia ($T_{A1}$)
- Time to level 2 analgesia ($T_{A2}$)
- Total amount of analgesic 1 consumption ($A_1$)
- Total amount of analgesic 2 consumption ($A_2$)
- Proportion of patients requiring analgesia (level 1 or level 2) in the first 2 h after surgery end ($\pi_{2h}$)
- Proportion of patients requiring analgesia (level 1 or level 2) in the first 4 h after surgery end ($\pi_{4h}$)
- Proportion of patients requiring analgesia (level 1 or level 2) from surgery end until eligibility for home discharge ($\pi_{ed}$)
- Proportion of patients requiring level 1 analgesia ($\pi_{A1}$) from surgery end until eligibility for home discharge
- Proportion of patients requiring level 2 analgesia ($\pi_{A2}$) from surgery end until eligibility for home discharge
- Time to first supplementary analgesia, other than the planned level 1 or 2 analgesia ($T_{ao}$)
- Proportion of patients requiring supplementary analgesia, other than the planned level 1 or 2 analgesia ($\pi_{ao}$)
- Time to rescue anaesthesia ($T_{ras}$)
- Proportion of patients requiring rescue anaesthesia ($\pi_{ras}$)
- Time to onset of spinal block (i.e. time to readiness for surgery) ($T_{rs}$)
- Maximum level of sensory block ($SB_{max}$)
- Time to maximum level of sensory block ($T_{SBmax}$)
- Time to regression of spinal block ($T_{reg}$) (defined as complete regression of sensory block to S1)
- Time to unassisted ambulation ($T_{ua}$)

- Time to first spontaneous urine voiding ($T_{uv}$)
- Time to eligibility for home discharge ($T_{ed}$)

### *9.1.3 Safety variables*

- Treatment-emergent adverse events throughout the study
- Incidence of neurological complications including TNS at 24 h post-dose and at day 7±1
- Vital signs (blood pressure, heart rate), $SpO_2$
- Concomitant medications

## 9.2 Efficacy assessments

### *9.2.1 Efficacy parameters*

Efficacy assessments are based on the primary and secondary efficacy variables listed in § 9.1 above. Assessment procedures are detailed in § 7.

## 9.3 Safety assessments

Patients will be questioned about the occurrence of treatment-emergent adverse events (TEAEs) throughout the study. Particular attention will be given to neurological complications including TNS symptoms. Further details on the AE assessments are given in § 7.2.

ECG at screening will be recorded only for patients > 60 years old. ECG, blood pressure, heart rate and $SpO_2$ will be monitored and assessed as detailed in § 7.1.1 and 7.1.2.
Occurrence of clinically relevant hypotension or bradycardia will be monitored throughout the study and, if observed, treated according to the hospitals' standard procedures.
Concomitant medication intake will be recorded.

# 10 STATISTICAL METHODS

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

Not available data will be evaluated as "missing values". The statistical analysis will be performed using SAS® system version 9.3 (TS1M1) (27) or higher for Windows (the actual version will be stated in the final clinical study report). Pain intensity AUCs will be calculated and analysed using WinNonlin® version 6.3 (28) or higher (the actual version will be stated in the final report).

## 10.1 Analysis Sets

### *10.1.1 Definitions*

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

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

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

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

- Enrolled set: all enrolled patients. This analysis set will be used for demographic and baseline characteristics.
- Full Analysis Set (FAS): all randomised patients who fulfil the study protocol requirements in terms of investigational product (i.e. paracetamol/placebo) administration and anaesthetic administration and have at least one post-baseline assessment of the primary efficacy evaluation (i.e. surgery-related pain at rest). This analysis set will be used for the sensitivity analysis and for the secondary efficacy analysis.
- Per Protocol set (PP): all randomised patients who fulfil the study protocol requirements in terms of investigational product administration, anaesthetic administration and primary efficacy evaluation (i.e. surgery-related pain at rest), with no major deviations that could affect the primary efficacy results. This analysis set will be used for the primary efficacy analysis and for the secondary efficacy analysis.
- Safety set: all patients who receive at least one dose of the investigational product and/or anaesthetic. This analysis set will be used for the safety analyses.

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

actually receive (Enrolled set, PP set and Safety set) and to the treatment they are assigned to (FAS).

### *10.1.2 Reasons for exclusion from the Full Analysis Set*

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

- failure to be administered the IMP or the NIMP
- lack of any primary efficacy data post enrolment

### *10.1.3 Reasons for exclusion from the Per Protocol set*

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

- lack of compliance to the IMP or to the NIMP (i.e. whole scheduled dose not administered)
- exposure to an IMP or NIMP different from the one assigned to the subject
- missing primary efficacy data
- failure to satisfy any inclusion/exclusion criteria (eligibility violations)

## 10.2 Sample size and power considerations

At least sixty (60) male/female patients (at least 15 patients per dose group), aged 18-80 years, scheduled for elective knee procedures up to 40 min duration (e.g. diagnostic knee arthroscopy and meniscectomy not requiring the micro-fracture technique) under spinal anaesthesia will be enrolled in order to have at least 15 treated patients per treatment group included in the Per Protocol Set. The sample size for the study is not based on any formal sample size calculation. The number of at least 15 treated patients/treatment group included in the Per Protocol Set is deemed appropriate considering the exploratory and descriptive nature of the study.

## 10.3 Demographic, baseline and background characteristics

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

## 10.4 Analysis of efficacy parameters

All study data will be listed by patient, treatment group and assessment time point/interval (if applicable) and will be summarised by treatment group and assessment time point/interval (if applicable) using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max) for quantitative variables and frequencies for qualitative variables. Summary statistics will be performed on the Per Protocol Set and on the Full Analysis Set.

### *10.4.1 Primary efficacy analysis*

The primary efficacy analysis will be performed on the Per Protocol Set.

Pain at rest (VAS scores at each pre-defined time point) will be analysed using rank-transformed repeated measures ANCOVA with rank-transformed baseline pain at rest as covariate, and treatment, assessment time point and treatment*assessment time point as fixed effect. Pairwise comparisons between treatment groups for pain at rest will be performed at a two-sided type I error $\alpha = 0.05$ according to the following hierarchical order:

1. P vs. D3 (90 mg)
2. P vs. D2 (60 mg)
3. P vs. D1 (30 mg)
4. D1 (30 mg) vs. D3 (90 mg)
5. D2 (60 mg) vs. D3 (90 mg)
6. D1 (30 mg) vs. D2 (60 mg)

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

### *10.4.2 Sensitivity analysis*

The primary efficacy analysis will be repeated on the Full Analysis Set. The same pairwise comparisons foreseen for the primary variable will be performed at a two-sided type I error $\alpha = 0.05$ according to the same hierarchical order.

### *10.4.3 Secondary efficacy analysis*

Due to the small sample size, collected data will be compared using nonparametric tests.
$T_{pa}$, $T_{A1}$, $T_{A2}$, $T_{ao}$, $T_{ras}$, $T_{rs}$, $T_{SBmax}$, $T_{reg}$, $T_{ua}$, $T_{uv}$ and $T_{ed}$ will be presented using Kaplan-Meier curves and will be compared between treatment groups by log rank test.
$A_1$, $A_2$, $AUC_{t1\text{-}t2}$ ($AUC_{0\text{-}2h}$, $AUC_{0\text{-}4h}$) and $AUC_{last}$ will be summarised by treatment group using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max).
$SB_{max}$, $\pi_{2h}$, $\pi_{4h}$, $\pi_{ed}$, $\pi_{A1}$, $\pi_{A2}$, $\pi_{ao}$ and $\pi_{ras}$ will be summarised by treatment group using frequency tables.
$SB_{max}$, $A_1$ and $A_2$ will be compared between treatment groups by Wilcoxon rank sum test.
$\pi_{2h}$, $\pi_{4h}$, $\pi_{ed}$, $\pi_{A1}$, $\pi_{A2}$, $\pi_{ao}$ and $\pi_{ras}$ will be compared between treatment groups using the Fisher exact test.
VAS scores for pain at rest $AUC_{t1\text{-}t2}$ ($AUC_{0\text{-}2h}$, $AUC_{0\text{-}4h}$) and $AUC_{last}$ will be analysed by rank-transformed ANOVA with treatment as fixed effect, and by ANOVA with treatment as fixed effect.

## 10.5 Safety and tolerability evaluation

- **AEs**

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

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

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarised by treatment and overall. The number and percentage of subjects with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity. For TEAEs that change severity during the study (e.g. from mild to moderate or from moderate to mild), the more severe intensity will be reported in the summary tables.

The Investigator will evaluate the reasonable possibility of a causal relationship with the study drug and any other causal relationship as follows:

- Relationship to investigational product (IMP)
- Other causal relationship
  - Not applicable
  - Relationship to study anaesthetic (NIMP)
  - Other

- **Physical examination**

Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed.

- **Vital signs and $SpO_2$**

Screening, baseline and final/early termination assessments of haemodynamic variables and any other assessment judged clinical significant will be reported in the CRF and listed in the clinical study report. Screening, baseline and before-discharge values of vital signs and $SpO_2$ will be summarised by descriptive statistics.

- **Body weight**

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

- **ECG**

ECG results at screening (when applicable) will be listed. ECG results during monitoring judged clinical significant will be reported in the CRF and listed in the clinical study report.

- **Incidence of neurological complications including TNS**

The incidence of neurological complications including TNS at 24 h post-dose and at day 7±1 (i.e. 6±1 days after analgesic/anaesthetic IT injection and surgery) will be summarised by treatment group and overall using tables of frequency.

# 11 DEFINITION AND HANDLING OF AES AND SAES

## 11.1 Applicable SOPs

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

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

## 11.2 Definitions

- **Adverse event (AE)**

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

- **Adverse Drug Reaction (ADR)**

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

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

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

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

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

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

- **Serious Adverse Event (SAE)**

Any untoward medical occurrence that at any dose:

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

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

- **Reference Safety Information (RSI)**: in order to assess whether an adverse reaction is expected, the Investigator's Brochure (IB) of the investigational product and the information leaflet of the NIMP will be used.

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

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

### 11.3 AEs monitoring window

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

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

### 11.4 AEs recording

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

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

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

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

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

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

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

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

**10.** Severity: the severity or intensity of the event
- 1 Mild
- 2 Moderate
- 3 Severe

**11.** Pattern: Used to indicate the pattern of the event over time
- 1 Single Event
- 2 Continuous
- 3 Intermittent

**12.** Serious Adverse Event

**13.** Action Taken with Study Drug: describes changes to the study drug as a result of the event. It is specifically for actions taken with the study drug
- 1 Dose Not Changed
- 2 Dose Increased
- 3 Dose Reduced
- 4 Drug Interrupted (i.e. temporary stop)
- 5 Drug Withdrawn (i.e. definitive stop)
- 6 Not Applicable (e.g. drug administration not started yet or completed)
- 7 Unknown

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

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

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

**17.** Outcome: Outcome of the event
- 1 Recovered/Resolved
- 2 Recovered/Resolved With Sequelae
- 3 Recovering/Resolving

- 4 Not Recovered/Not Resolved
- 5 Fatal
- 6 Unknown

## 11.5 SAEs reporting

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

## 11.6 SUSARs management

The clock for initial expedited reporting starts as soon as the information containing the minimum reporting criteria has been received by the sponsor (day 0).
For fatal and life-threatening SUSARs the EC and Competent Authority (CA) should be informed as soon as possible and in any case within 7 days.
If the initial report is incomplete, e.g. not all the information/assessments were available, a complete report should be sent within an additional 8 days.
SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

The minimum information to be reported includes:

- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect IMP (including active substance name, code)
- A causality assessment (a reasonable possibility of a causal relationship with the study drug can be excluded only if there is information supporting this decision, otherwise it cannot be excluded).

### 11.7 Other events qualified for expedited reporting

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

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

### 11.8 SAEs: contacts

SAEs must be reported on SAE reporting forms and faxed/emailed within 24 H to Corporate Drug Safety Unit of the sponsor - contact details below:

| | |
|---|---|
| Fax: | +41(0)91.646.85.61 |
| Phone: | +41(0)91.640.42.50 |
| Email: | corporate_drug_safety@sintetica.com |

# 12 DATA MANAGEMENT PROCEDURES

## 12.1 Data collection – CRFs

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

## 12.2 Unique subject identifier

All the subjects who sign the informed consent form for the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique subject identifier consists of the sponsor study code (i.e. PAR.3-01-2017), the 3-digit centre number (i.e. 001), the 4-digit screening number (e.g. S001, S002, etc.) and, if applicable, the 3-digit subject randomisation number (i.e. 001, 002 .., 060). Study code, centre number, screening number and subject randomisation number are separated by slashes ("/"). The last 8 digits of the unique subject identifier (enrolled subjects), corresponding to the subject screening and subject randomisation numbers separated by a slash, will appear as subject identifier in the individual listings and figures of the clinical study report and will be used to identify the subjects in in-text tables or wording (if applicable).

## 12.3 Database management

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

### *12.3.1 Coding dictionaries*

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

# 13 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

## 13.1 Monitoring

The monitoring visits will be conducted by appropriate staff of CROSS Research S.A. (see § 16.3) and of the Sponsor. Two monitors will be involved: one monitor will perform the checks of the study evaluations and procedures and will not be involved in the drug accountability. A second monitor will be defined before the start of the study and will be responsible for performing the drug accountability. He/she will not be involved in other monitoring activities. This will be done to safeguard the double-blind. Due care will be applied in order to avoid any disclosure of unblinded information to blind staff.

Monitoring activities, including monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures and monitoring reports will comply with ICH-GCP chapter 5.18 requirements. Monitoring activities will be detailed in the monitoring plan.

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

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

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

## 13.2 Quality Control and Quality Assurance

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

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

The CRO and the sponsor will be responsible for their respective activities.

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

### 13.3 Applicable SOPs

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

### 13.4 Data access

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

### 13.5 Audits and inspections

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

The study may also be inspected by regulatory authorities.

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

# 14 ETHICAL CONSIDERATIONS

## 14.1 Ethics and Good Clinical Practice (GCP)

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

The approval of the study protocol by the local (Canton Ticino) IEC and by the Federal Health Authorities (Swissmedic) will be obtained before the start of the study.

The present clinical study will be carried out according to the general principles of the current revision of Good Clinical Practice (GCP), ICH Topic E6 (R2), and the applicable local law requirements.

## 14.2 Informed consent

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

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

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

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

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

## 14.3 Insurance policy

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

## 14.4 Withdrawal of subjects

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

### *14.4.1 Discontinuation type*

- **Discontinuation from data collection**: the subject discontinues from the collection of primary and secondary endpoints
- **Discontinuation from interventions and data collection**: the subject discontinues from the intake of the IMP(s) and/or NIMP and from the collection of primary and secondary endpoints

### *14.4.2 Primary reason for discontinuation*

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

- **other**: different than the ones previously specified

### *14.4.3 Discontinuation procedures*

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

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

Subjects discontinued after paracetamol and anaesthetic spinal injection will not be replaced, whilst subjects discontinued before paracetamol and anaesthetic spinal injection can be replaced in order to have 15 administered patients per dose group.

## 14.5 Study termination

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

Reasons for discontinuation have to be documented appropriately.

# 15 ADMINISTRATIVE PROCEDURES

## 15.1 Material supplied to the clinical centre

Beside IMPs and NIMP, the following study material will be supplied to the clinical centre:

- final version of the study protocol
- CRF for each subject plus some spare copies
- copy of the investigator's brochure (IB) and Summary of Products Characteristics relative to the IMP and NIMP, respectively
- informed consent forms

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

## 15.2 Protocol amendments

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

All amendments will be sent to the EC and Swissmedic, as applicable.

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

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

## 15.3 Study documentation and record keeping

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

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

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

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

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

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

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

### 15.4 Study subjects' recruitment

Study participants will be recruited at the clinical centre among the patients attending the clinic for knee procedures up to 40 min duration (e.g. diagnostic knee arthroscopy and meniscectomy not requiring the micro-fracture technique).

### 15.5 Confidentiality and data protection

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

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

### 15.6 Publication policy

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

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

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

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

According to The Federal Act on Research involving Human Beings and the Ordinance on Clinical Trials in Human Research, the study will be registered and published in a WHO primary register or clinicaltrials.gov as well as in the supplementary federal database.

# 16 STUDY RESPONSIBLE PERSONS

## 16.1 Sponsor

Sintetica S.A., Via Penate 5, CH-6850 Mendrisio, Switzerland
Phone: +41.91.640.42.50
Fax: +41.91.646.85.61

**Sponsor representatives**
**Clinical Project Leader**
Elisabetta Donati, Corporate Director Scientific Affairs
Email: edonati@sintetica.com

**Medical Expert**
Dr. Claudio Camponovo, Department of Anaesthesiology, Clinica Ars Medica, Switzerland
(*for the complete address and contact details, please see clinical centre below*)

## 16.2 Institutes performing the study

### *16.2.1 Clinical centre*

Department of Anaesthesiology, Clinica Ars Medica, Via Cantonale, CH-6929 Gravesano, Switzerland
Phone: +41.91.611.6211
Fax: +41.91.605.1559

**Principal investigator**
Claudio Camponovo, MD. Chairman of the Department of Anaesthesiology
Email: ccamponovo@arsmedica.ch

## 16.3 Co-ordination, monitoring, data analysis & reporting

CROSS Research S.A. and CROSS Metrics S.A., Switzerland, sister companies, share the same standard operating procedures and quality assurance system

CROSS Research S.A., Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
Phone: +41.91.6300510
Fax: +41.91.6300511

**Coordination**
Emanuela Terragni, Clinical Project Leader
Email: projectmanagement@croalliance.com

**Medical Writing Representative**
Chiara Leuratti, Clinical Projects Unit Head
Email: medicalwriting@croalliance.com

**Biometry Unit Representative**
Matteo Rossini, Biometry Manager, Unit Head
Email: statistics@croalliance.com

**Quality Assurance Unit Representative**
Mario Corrado, Quality Assurance Manager, Unit Head
Email: qau@croalliance.com

**Monitoring**
Chiara Castiglioni, Clinical Research Associate and Clinical Trial Assistant
Email: projectmanagement@croalliance.com

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# 18 APPENDICES

## 18.1 Neurological complications (including TNS) questionnaires

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Contract Research Organisation for Scientific Services

*CONFIDENTIAL*

*Study code CRO-17-133*
*Sponsor code PAR.3-01-2017*
*Paracetamol/Chloroprocaine IT*
*Final version 1.0, 16OCT2017*

Centre Nr |_0_|_0_|_1_| Screening Nr S|_ _|_ _ _| Randomisation Nr |_ _|_ _ _|

**NEUROLOGICAL COMPLICATIONS**
**(including TRANSIENT NEUROLOGICAL SYMPTOMS)**
**POST-OPERATIVE SURVEY - 24 HOURS AFTER INJECTION**

Questionnaire start date/time |_ _|_ _|_ _ _|_ _|_ _|_ _|_ _| |_ _|_ _|:|_ _|_ _|

Sex ☐ Female ☐ Male

Are you feeling good? ☐ Y ☐ N

If No, do you experience any of the following? ☐ Fatigue ☐ Nausea/Vomiting ☐ Dizziness ☐ Difficulty Urinating or Defecating

Pain at the site of injection in the 24 hours after analgesic/anaesthetic IT injection and surgery?

☐ Y ☐ N *(if No, the following score must be '0')*

If 0 is no pain and 10 is the worst imaginable pain, how would you rate your average pain at the site of injection in the 24 hours after analgesic/anaesthetic IT injection and surgery?

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

Surgery-related pain in the 24 hours after analgesic/anaesthetic IT injection and surgery?

☐ Y ☐ N *(if No, the following score must be '0')*

If 0 is no pain and 10 is the worst imaginable pain, how would you rate your average surgery-related pain in the 24 hours after analgesic/anaesthetic IT injection and surgery?

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

Unusual sensations? ☐ Y ☐ N

If Yes, Characteristic of these sensations ☐ Burning ☐ Tingling ☐ Dull ☐ Aching ☐ Numbness ☐ Hypoesthesia ☐ Others _____

Location of these symptoms ☐ Buttocks ☐ Thighs anterior ☐ Thighs posterior ☐ Lower limbs ☐ Sacrum ☐ Calves ☐ Back

Laterality of these symptoms ☐ One sided ☐ Bilateral

Have you ever experienced such symptoms in your life before? ☐ Y ☐ N

Investigator's Signature: _____

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*Sponsor code PAR.3-01-2017*
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Centre Nr |0|0|1| Screening Nr S|__|__| Randomisation Nr |__|__|

## NEUROLOGICAL COMPLICATIONS (including TRANSIENT NEUROLOGICAL SYMPTOMS) POST-OPERATIVE SURVEY - FOLLOW-UP - DAY 7±1

Questionnaire start date/time |__|__|-|__|__|__|-|__|__|__|__| |__|__|:|__|__|

Sex ☐ Female ☐ Male

Are you feeling good? ☐ Y ☐ N

If No, do you experience any of the following? ☐ Fatigue ☐ Nausea/Vomiting ☐ Dizziness ☐ Difficulty Urinating or Defecating

Pain at the site of injection in the 6±1 days after analgesic/anaesthetic IT injection and surgery?

☐ Y ☐ N *(if No, the following score must be '0')*

If 0 is no pain and 10 is the worst imaginable pain, how would you rate your average pain at the site of injection in the 6±1 days after analgesic/anaesthetic IT injection and surgery?

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

Surgery-related pain in the 6±1 days after analgesic/anaesthetic IT injection and surgery?

☐ Y ☐ N *(if No, the following score must be '0')*

If 0 is no pain and 10 is the worst imaginable pain, how would you rate your average surgery-related pain in the 6±1 days after analgesic/anaesthetic IT injection and surgery?

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

Unusual sensations? ☐ Y ☐ N

If Yes, Characteristic of these sensations ☐ Burning ☐ Tingling ☐ Dull ☐ Aching ☐ Numbness ☐ Hypoesthesia ☐ Others _____

Location of these symptoms ☐ Buttocks ☐ Thighs anterior ☐ Thighs posterior ☐ Lower limbs ☐ Sacrum ☐ Calves ☐ Back

Laterality of these symptoms ☐ One sided ☐ Bilateral

Have you ever experienced such symptoms in your life before? ☐ Y ☐ N

Investigator's Signature: _____