Study CRO-15-126 - Sponsor code PAR.3/02-2015

Dose-finding study of intrathecal paracetamol administered immediately before spinal anaesthesia in patients scheduled for hip replacement surgery

Prospective, single centre, randomised, parallel-group, double-blind, placebo-controlled, three doses of intrathecal paracetamol, 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
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Development phase:	Phase II
Version and date:	Final version 1.0, 01DEC15

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

This document comprises 74 pages

PROTOCOL APPROVAL

SPONSOR
Sintetica S.A., Switzerland

Clinical Project Leader
Elisabetta Donati, Corporate Director Scientific Affairs

01 DEC 2015
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.

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STUDY SYNOPSIS

Title: Dose-finding study of intrathecal paracetamol administered immediately before spinal anaesthesia in patients scheduled for hip replacement surgery
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Clinical phase: Phase II
Study design: Prospective, single centre, randomised, parallel-group, double-blind, placebo-controlled, three doses of intrathecal paracetamol, 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 medicinal product (IMP): Paracetamol 3% (30 mg/mL), solution for injection, Sintetica S.A., Switzerland. Three doses of the paracetamol solution, administered by intrathecal injection, will be investigated in the study. A fourth treatment group will only receive a placebo solution. ➢ D1: 60 mg Paracetamol 3% (2 mL) ➢ D2: 90 mg Paracetamol 3% (3 mL) ➢ D3: 120 mg Paracetamol 3% (4 mL) ➢ P: Placebo (0.9% saline solution) (2 mL, 3 mL and 4 mL) ***Other products (Non-investigational medicinal product, NIMP)*** Hyperbaric Bupivacaine HCl 0.5% (5 mg/mL), injectable solution, Sintetica S.A., Switzerland, will be administered by intrathecal injection to all patients in the 4 treatment groups, at the dose of either 12.5 mg (2.5 mL, patient's height ≤160 cm) or 15 mg (3 mL, patient height > 160 cm). The anaesthetic will be administered immediately after intrathecal paracetamol administration (maximal interval between administrations: 2 min).
Dose regimen: Patients scheduled for hip replacement surgery 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 placebo solution (P) by intrathecal (IT) injection. Immediately after paracetamol or placebo IT administration, all patients will receive a single IT dose of Hyperbaric Bupivacaine HCl 0.5% (12.5 mg for ≤ 160 cm-tall patients and 15 mg for > 160 cm-tall patients). The time interval between paracetamol IT and bupivacaine IT administrations should not exceed 2 min. Administrations' times will be recorded. Postoperatively all patients will have access to morphine via a patient controlled analgesia (PCA) pump with a standard programme (1-mg bolus, 5-min lock-out interval, no 4-h dose limit).
Objective: The objective of the 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 solution, for post-operative analgesia of hip replacement surgery performed under spinal anaesthesia.
End-points: **Primary end-point:** ➢ Pain intensity at rest at 1, 2, 3 h and then every 3 h up to 48 h after anaesthetic IT injection (time 0h), using a 0-100 mm VAS. **Secondary end-points:** ➢ Total morphine use in the first 24 h, in the first 48 h and in the entire study period ➢ Time to first morphine use ➢ Need for supplementary analgesia, other than the planned morphine PCA (i.e. other narcotic or analgesic) ➢ Time to first supplementary analgesia, other than the planned morphine PCA

STUDY SYNOPSIS (cont.)

Secondary end-points, continued:

- Functional assessment reflecting post-operative recovery status, in terms of: Nocturnal awakenings due to pain; Time to gastro-intestinal (GI) motility (return of bowel sounds, flatulence or bowel movement); Need for postoperative urinary indwelling catheter after initial removal of surgical catheter; Resumption of ambulation; Resumption of liquid intake and solid diet; Length of hospital stay
- Morphine-related adverse events (Diffuse pruritus, overt respiratory depression requiring treatment, Post-operative vomiting or need for anti-emetic medication, Sedation and combined safety assessment)
- Onset of spinal block (i.e. readiness for surgery)
- Maximum level of sensory block
- Time to maximum level of sensory block
- Regression of spinal block

Safety monitoring

Safety will be monitored throughout the study as follows:

- Treatment-emergent adverse events, including morphine-related adverse events (see above) and transient neurological symptoms (TNS);
- Routine monitoring (vital signs, SpO_2 and ECG)
- Concomitant medications
- Transfusion monitoring
- Routine safety laboratory tests at screening and final visit. Blood cell count on Day 2

Study variables:

Primary efficacy variable:

- Pain at rest VAS scores at screening, baseline (0 h), 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 h after anaesthetic IT injection and at discharge, using a 0-100 mm VAS.

Secondary efficacy and safety variables:

- Pain at rest VAS scores AUC_{t1-t2} (0-12h, 12-24h, 24-48h [if applicable] intervals), where AUC_{t1-t2} is defined as the area under the pain intensity curve at the specified time-intervals
- Total morphine use in the first 24 h, in the first 48 h and in the entire study period
- Time to first morphine use
- Proportion of patients requiring supplementary analgesia
- Time to first supplementary analgesia
- Functional assessment variables (reflecting post-operation recovery status):
  - Nocturnal awakenings due to pain (number of events, proportion of patients)
  - Time to GI motility (every 6 h; return of bowel sounds, flatulence or bowel movement)
  - Need for postoperative urinary indwelling catheter after initial removal of surgical catheter (proportion of patients)
  - Time to resumption of ambulation
  - Time to resumption of liquid intake and solid diet
  - Time to home discharge (Length of hospital stay)
- Morphine-related adverse events:
  - Diffuse pruritus,
  - Overt respiratory depression requiring treatment,
  - Post-operative vomiting or need for anti-emetic medication,
  - Sedation, defined as score ≤ -3 on the Richmond Agitation Sedation Scale (RASS)
  - Combined Safety Assessment (defined as the summary of the binary occurrences of any of the events listed above during the first 48 h)
- Treatment-emergent adverse events, including morphine-related adverse events (see above) throughout the study
- Incidence of transient neurologic symptoms (TNS) at day 6±1
- Vital signs (blood pressure, heart rate and peripheral oxygen saturation [SpO_2]) and ECG
- Concomitant medications
- Time to onset of spinal block (i.e. time to readiness for surgery)
- Maximum level of sensory block
- Time to maximum level of sensory block
- Time to regression of spinal block
- Safety laboratory tests parameters

STUDY SYNOPSIS (cont.)

Sample size:
At least sixty (60) male/female patients (15 patients per dose group), aged 18-80 years, scheduled for hip replacement surgery under spinal anaesthesia with anticipated need for post-operative narcotic analgesia, who have adequate i.v. access and anticipated hospital stay > 48 hours will be enrolled in order to have 15 treated patients per treatment group.

The sample size for the study is not based on any formal sample size calculation. The number of 15 treated patients/treatment group 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 18-80 years (inclusive) old patients, scheduled for hip replacement surgery, with anticipated need for post-operative narcotic analgesia, adequate i.v. access and anticipated hospital stay > 48 hours.
3. *Body Mass Index (BMI)*: 18 - 34 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. *Pain assessment*: anticipated to be unable to make a reliable self-report of pain intensity
5. *Allergy*: ascertained or presumptive hypersensitivity to the active principles (paracetamol and/or amide type anaesthetics) and/or formulations' ingredients or related drugs, opioids, non-steroidal anti-inflammatory drugs; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers could affect the outcome of the study
6. *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 asthma or 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.
7. *Liver function*: Impaired liver function (transaminases > twice upper limit)
8. *Renal function*: Renal dysfunction (creatinine > 2.0 mg/dL)
9. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study, calculated from the first day of the month following the last visit of the previous study
10. *Drug, alcohol*: history of drug or alcohol abuse. Pre-existing dependence on narcotics or known tolerance to opioids
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)]*
12. *Chronic pain syndromes*: patients with chronic pain syndromes (taking opioids, anticonvulsant agents or chronic analgesic therapy).
13. *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 1 week before the start of the study and during the study. Hormonal contraceptives for females are allowed.

Study schedule:
The study will include a screening phase (Visit 1, Days -21/1), a treatment phase (paracetamol IT administration, anaesthesia and surgical procedure: Visit 2, Day 1) and a follow-up phase including an observation period (Visit 3, from Day 1 after surgery until discharge, a final visit (at discharge) and a follow-up (day 6±1).

STUDY SYNOPSIS (cont.)

Study schedule, continued:
Screening Phase (Visit 1, Day -21/-1): Patients scheduled for hip replacement surgery will be informed about the aims, procedures and possible risks of the study and will be asked to sign the informed consent form for the inclusion in the trial. Routine pre-surgery assessments, including safety laboratory tests, 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, lifestyle, physical abnormalities, body weight, height, vital signs, peripheral oxygen saturation (SpO_2) and ECG, medical/surgical history and previous/concomitant medications. Pain history and pain intensity at rest (measured using a 100 mm VAS) will also be recorded at screening.
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 the placebo solution by IT injection.
Blood pressure, heart rate, SpO_2 and ECG (if foreseen by the hospital procedures) will be monitored at baseline and during block placement using standard monitors. Before any procedure, patients will be pre-medicated with propofol (1-2 mg/kg/h); in addition, an antibiotic will be administered. Ringer's solution will be infused from the beginning of surgery until patient's discharge from the recovery room. Pain intensity will be measured at baseline using a 100 mm VAS (see *Efficacy assessments* below).
Paracetamol or placebo will be administered intrathecally (IT) just before spinal anaesthesia.
For the intrathecal injection of the analgesic/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 Reganesth or Nizell needle; caudocranial direction of the bevel) 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 in the lateral decubitus position (or sitting, if more appropriate) using a midline approach at the L3/L4 or L4/L5 interspaces. After the lumbar puncture and after verifying the spontaneous flow of liquor at the beginning and at the end of the procedure, two short aspirations will be done to verify the proper positioning of the needle. Barbotage must be avoided.
After intrathecal administration of the paracetamol dose or placebo, the anaesthetic (Hyperbaric bupivacaine HCl 0.5%) 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 bupivacaine IT administration will be recorded in the case report form (CRF). Before the block (pre-dose assessment), as already reported above, and during the spinal block every 10 min until the end of anaesthesia, hemodynamic variables (HR, BP, SpO_2; ECG if available) will be monitored according to the hospital standard procedures.
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 discharge)
Postoperatively all patients will have access to morphine via a PCA device with a standardised programme (1 mg/mL, 1-mg bolus, 5-min lock out time interval, no 4-h dose limit). If adequate pain relief is not achieved with the i.v. PCA device alone, supplemental rescue boluses of i.v. morphine or another analgesic (according to the Investigator's opinion) will be administered as needed, according to the standard hospital procedures.
In the morning of the first postoperative day (24 h post-dose), laboratory tests (blood cell count) will be performed.

Efficacy and safety assessments
In the morning of the first postoperative day (24 h post-dose) after completion of the routine nursing activities, the PCA device will be temporarily discontinued and the total amount of morphine administered to the patient recorded. Total amount of administered morphine via the PCA device will also be recorded at 48 h and for the entire study period. Details on rescue medication and time to rescue medication (i.v. morphine or another analgesic) will also be recorded.

Pain intensity at rest will be recorded, using a 0-100 mm VAS, at pre-specified time points, i.e. at baseline (0), 1, 2, 3 h and then every 3 h up to 48 h after anaesthetic IT injection.

STUDY SYNOPSIS (cont.)

Study schedule, continued

Efficacy and safety assessments, continued

Treatment-emergent adverse events will be recorded and treated according to the standard procedures of the hospital. Particular attention will be given to the occurrence of nausea, vomiting, sedation, pruritus and respiratory depression as well as to the occurrence of paraesthesia, headache, miction/defecation difficulties, tiredness, vertigo and TNS.

To measure the agitation/sedation status of patients, the Richmond agitation-sedation scale will be used (Curtis N *et al.* American Journal of Respiratory and Critical Care Medicine 2002;166(10):1338-44).

GI motility will be assessed every 6 h until return of bowel sounds, flatulence or bowel movement, and recorded in the CRF. All primary and secondary study variables will be recorded.

Follow-up Phase - Discharge (final visit)

Patients will stay in the hospital until the criteria for discharge are met according to the investigator's opinion and the hospitals' standard procedures. Before discharge they will undergo a final visit (or early termination visit [ETV] in case of premature discontinuation from the study). Day and time of discharge from the hospital will be recorded.

Follow-up Phase - Follow-up: On Day 6±1 (i.e. 5±1 days after analgesic/anaesthetic IT injection and surgery), the investigator or his deputy will question patients about symptoms of TNS and unusual sensations not associated with the operation area (buttock, thigh posterior, thigh anterior, lower limb, sacrum, calves, other areas) following prepared questions.

Data analysis:

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

Definition of analysis sets:

Enrolled Set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics.

Full Analysis Set (FAS): all randomised patients who fulfil the study protocol requirements in terms of investigational product (i.e. paracetamol/placebo) and anaesthetic administration and have at least one post-baseline assessment of the primary efficacy evaluation (i.e. 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. 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.

Efficacy analysis

All study data will be listed by patient, treatment group and assessment time point/evaluation interval (if applicable) and will be summarised by treatment group and assessment time point/evaluation interval (if applicable) using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max) for quantitative variables and tables of frequencies for qualitative variables. Summarisation 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 will be analysed using a 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 (120 mg)
2. P vs. D2 (90 mg)
3. P vs. D1 (60 mg)
4. D1 (60 mg) vs. D3 (120 mg)
5. D2 (90 mg) vs. D3 (120 mg)
6. D1 (60 mg) vs. D2 (90 mg)

STUDY SYNOPSIS (cont.)

Data analysis, continued:

Primary efficacy analysis, continued

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

All the analyses on the secondary variables will be performed with a nominal two-sided type I error $\alpha = 0.05$.
The same pairwise comparisons foreseen for the primary variable will be performed.

As secondary efficacy analysis, pain at rest will be analysed using a repeated measures ANCOVA with baseline pain at rest as covariate and treatment, assessment time point and treatment*assessment time point as fixed effect.

Pain at rest VAS scores $AUC_{t1\text{-}t2}$ (0-12h, 12-24h, 24-48h intervals) will be analysed using a rank-transformed ANOVA with treatment as fixed effect. Different analyses will be performed for the $AUC_{t1\text{-}t2}$ (0-12h), $AUC_{t1\text{-}t2}$ (12-24h) and $AUC_{t1\text{-}t2}$ (24-48h).

Pain at rest VAS scores $AUC_{t1\text{-}t2}$ (0-12h, 12-24h, 24-48h intervals) will be analysed using an ANOVA with treatment as fixed effect. Different analyses will be performed for the $AUC_{t1\text{-}t2}$ (0-12h), $AUC_{t1\text{-}t2}$ (12-24h) and $AUC_{t1\text{-}t2}$ (24-48h)

Total amount of morphine used in the first 24 h, in the first 48 h and in the entire study period will be analysed using a rank-transformed ANOVA with treatment as fixed effect. Different analyses will be performed for the amount used in the first 24 h, in the first 48 h and in the entire study period.

Total amount of morphine used in the first 24 h, in the first 48 h and in the entire study period will be analysed using an ANOVA with treatment as fixed effect. Different analyses will be performed for the amount used in the first 24 h, in the first 48 h and in the entire study period.

Time to first morphine use will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

Proportion of patients in need of narcotics other than morphine or in need of other rescue analgesics will be compared between treatment groups by Fisher's exact test.

Time to first subsequent analgesia (narcotic or NSAIDs) will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

Proportion of patients with nocturnal awakenings due to pain will be compared between treatment groups by Fisher's exact test. The same pairwise comparisons foreseen for the primary variable will be performed.

Number of nocturnal awakenings due to pain will be compared between treatment groups by Wilcoxon rank-sum test.

Time to GI motility will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

Proportion of patients who need postoperative urinary indwelling catheter after initial removal of surgical catheter will be compared between treatment groups by Fisher's exact test.

Time to resumption of ambulation will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

Time to resumption of liquid intake and solid diet will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

STUDY SYNOPSIS (cont.)

Data analysis, continued:

Secondary efficacy analysis, continued

Time to home discharge will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

Proportion of patients with morphine-related adverse events will be compared between treatment groups by Fisher's exact test.

Time to onset of spinal block will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

The maximum level of sensory block will be compared between treatment groups by Wilcoxon rank-sum test.

Time to maximum level of sensory block will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

Time to regression of spinal block will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

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 tables of frequencies for qualitative variables.

STUDY SCHEDULE

Visit	Visit 1 Day -21/-1	Visit 2 Day 1	Follow-up phase		
			Observation period *From end of surgery to discharge**	Final visit/ETV[5]	Day 6±1
Informed consent	X				
Demography and lifestyle	X				
Medical/surgical history	X				
Physical examination	X				
Pain history and pain intensity	X				
Previous and concomitant medication	X	X	X		X
Height	X				
Body weight	X				
Vital signs (blood pressure, heart rate)[1]	X	X	X	X	
SpO_2[1]	X	X	X	X	
ECG[1]	X	X	X	X	
Laboratory tests[2]	X		X	X	
Pregnancy test (urine)[3]	X				
Inclusion/exclusion criteria	X	X			
Enrolment and Randomisation		X			
Propofol premedication		X			
Antibiotic		X			
Ringer's solution infusion - premedication		X			
Paracetamol IT administration		X			
Bupivacaine IT administration		X			
Blocks assessment		X	X		
Hip replacement surgery		X			
Pain intensity (VAS)		X[4]	X[4]	X[4]	
Morphine use assessment		X	X		
TNS questionnaire				X	X
Adverse events monitoring	X	X	X	X	X
Morphine-related AEs[6]			X	X	X
Functional assessment[7]		X	X	X	
Transfusion monitoring[8]		X	X		

**Observation period from the end of surgery to home discharge.*
The minimum duration of the observation period will be 48 h. During the observation period, efficacy assessments and safety monitoring according to the protocol and standard safety monitoring procedures of the hospital. Home discharge according to the investigator's opinion and standard hospital procedures

1. *Vital signs, SpO_2 and ECG (as foreseen by the standard hospital procedures) at screening, at baseline (before the spinal injection, then every 10 min from spinal injection until the end of the anaesthesia, according to the hospital standard procedures*
2. *Laboratory tests at screening and before discharge (final visit) according to the hospital procedures. In the morning of the post-operative day (day 2) complete blood cell count according to the hospital procedures.*

3. *Pregnancy test performed only for patients who cannot exclude a pregnancy*
4. *Pain intensity at rest will be recorded using a 0-100 mm VAS at baseline (0 h), 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 h after anaesthetic IT injection and at discharge*
5. *Patients will be discharged after the hospital criteria for discharge are met (final visit) and according to the hospital's standard procedures. In case of discontinuation, subjects will undergo an early termination visit (ETV)*
6. *Assessment of morphine-related side effects: diffuse pruritus, overt respiratory depression, post-operative vomiting or need for anti-emetic medication, sedation (defined as score ≤-3 on the RASS)*
7. *Functional assessment (post-operative recovery status): Nocturnal awakenings due to pain (number of events, proportion of patients), Time to GI motility (every 6 h; return of bowel sounds, flatulence or bowel movement), Need for postoperative urinary indwelling catheter after initial removal of surgical catheter, Resumption of ambulation, Resumption of liquid intake and solid diet, Home discharge time (Length of hospital stay)*
8. *According to the standard hospital's procedures*

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TABLES

FIGURES

LIST OF ABBREVIATIONS

β-HCG	human chorionic gonadotropin β
γ-GT	γ-Glutamyl transpeptidase
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	60 mg Paracetamol 3% (2 mL)
D2	90 mg Paracetamol 3% (3 mL)
D3	120 mg Paracetamol 3% (4 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)
PCA	Patient-controlled analgesia
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
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), also commonly known as acetaminophen in USA, is an active ingredient possessing analgesic and antipyretic activity used widely in medical practice to alleviate acute and chronic pain and to reduce the body temperature when this exceeds physiological values (1).

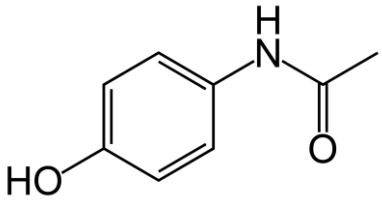

Figure 1.1.1.1 Paracetamol molecular structure

Paracetamol, conversely to the majority of commonly used analgesic drugs, is not an NSAID (non-steroidal anti-inflammatory drug), since it is almost devoid of antiaggregant and anti-inflammatory activity. To date, its mechanism of action remains little known, although this 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. 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 Analgesia for post-operative pain in combination with spinal anaesthesia

In medical practice, it has been observed that, in order to obtain a suitable post-surgical analgesic effect, it is necessary to administer analgesics in high quantities or, alternatively, to resort to the administration of opioid drugs (3,11).
Both of these therapeutic approaches expose patients to a series of possible side effects varying in accordance with the type and quantity of drug administered. Using opioids alone intensifies their side-effect profile that includes respiratory depression, postoperative nausea and vomiting, over-sedation, and pruritus.

Recently, there has been increased interest towards multimodal analgesia for postoperative pain control in order to reduce opioid related side effects and provide better patient

satisfaction (12). Maund *et al.* found that there is a decrease in 24 h morphine consumption when paracetamol, NSAIDs or COX-2 inhibitors are given in addition to morphine patient-controlled analgesia (PCA) after surgery (13, 14).

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 for the treatment of postsurgical pain (10). The formulation intrathecally injected alone or before loco-regional anaesthesia is intended to give an effective analgesia for post-surgical pain.

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, 15-18).
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.

1.2 Rationale

Administration of paracetamol for postoperative pain management using methods alternative to the traditional oral or iv routes is still to be explored in humans.

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.

The present study is being conducted to investigate the effectiveness of the novel supersaturated aqueous solution of paracetamol (Paracetamol 3% Sintetica), administered at 3 different doses, in reducing the post-operative pain in patients undergoing hip replacement surgery under spinal anaesthesia. Spinal anaesthesia will be performed according to the standard hospital procedures using Hyperbaric Bupivacaine (19). Bupivacaine is a well-known long-acting anaesthetic agent of the amide type for intrathecal (subarachnoid) anaesthesia, commonly used for urological and lower limb surgery lasting 1.5 - 3 hours and for abdominal surgery lasting 1.5 – 2 hours (20).

The doses of intrathecal Paracetamol 3% investigated in the present study, i.e. 60 mg, 90 mg and 120 mg, 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). The paracetamol doses of

the present study are 8 – 17 times lower than the doses normally administered in humans by the oral or i.v. route for post-operative pain control.

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 bupivacaine 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.

Bupivacaine has been on the market under different brand names in Switzerland, EU and USA for many years for the proposed indication and is routinely used as loco-regional anaesthetic in the surgical procedure performed in the study. Adverse reactions following Bupivacaine intrathecal injection could be caused by the drug or by the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia, temporary urinary retention), events caused directly (e.g. spinal haematoma) or indirectly (e.g. meningitis, epidural abscess) by needle puncture or events associated to cerebrospinal leakage (e.g. postdural puntural headache). Bupivacaine systemic adverse reactions are numbness of tongue, light-headedness, dizziness and tremors, followed by convulsions and cardiovascular disorders.

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 of hip replacement surgery performed under spinal anaesthesia.

2.1 Primary end-point

- Pain intensity at rest at 1, 2, 3 h and then every 3 h up to 48 h after anaesthetic IT injection (time 0h), using a 0-100 mm VAS.

2.2 Secondary end-points

- Total morphine use in the first 24 h, in the first 48 h and in the entire study period
- Time to first morphine use
- Need for supplementary analgesia, other than the planned morphine PCA (i.e. other narcotic or analgesic)
- Time to first supplementary analgesia, other than the planned morphine PCA
- Functional assessment reflecting post-operative recovery status, in terms of:
  - Nocturnal awakenings due to pain
  - Time to gastro-intestinal (GI) motility (return of bowel sounds, flatulence or bowel movement)
  - Need for postoperative urinary indwelling catheter after initial removal of surgical catheter
  - Resumption of ambulation
  - Resumption of liquid intake and solid diet
  - Length of hospital stay
- Morphine-related adverse events: Diffuse pruritus, Overt respiratory depression requiring treatment, Post-operative vomiting or need for anti-emetic medication, Sedation (Richmond Agitation Sedation Scale [score $\leq$ -3]) and Combined safety assessment.
- Onset of spinal block (i.e. readiness for surgery)
- Maximum level of sensory block
- Time to maximum level of sensory block
- Regression of spinal block

Safety monitoring
Safety will be monitored throughout the study as follows:
- Treatment-emergent adverse events, including morphine-related adverse events (see above) and transient neurological symptoms (TNS);
- Routine monitoring (vital signs, SpO_2 and ECG)
- Concomitant medications
- Transfusion monitoring
- Routine safety laboratory tests at screening and final visit. Blood cell count on Day 2

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)
Dose	D1: 2 mL corresponding to 60 mg paracetamol D2: 3 mL corresponding to 90 mg paracetamol D3: 4 mL corresponding to 120 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	2, 3 or 4 mL
Administration route	Intrathecal

3.1.1.3 NIMP (Non investigational medicinal product)

Product name	Hyperbaric Bupivacaine HCl 0.5% (5 mg/mL)
Manufacturer and Supplier	Sintetica S.A., Switzerland
Pharmaceutical form	Solution for injection (4-mL ampoule)
Dose	Patient height ≤ 160 cm: 12.5 mg (2.5 mL) Patient height > 160 cm: 15 mg (3 mL)
Administration route	Intrathecal

3.1.2 Dose regimen

Patients scheduled for hip replacement surgery will be randomised into four treatment groups (15 patients/group) to receive either one of 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 of the study.

In detail:

- Patients in D1 group will receive a single dose of 2 mL Paracetamol 3% (corresponding to 60 mg paracetamol).
- Patients in D2 group will receive a single dose of 3 mL Paracetamol 3% (corresponding to 90 mg paracetamol).
- Patients in D3 group will receive a single dose of 4 mL Paracetamol 3% (corresponding to 120 mg paracetamol).

- Patients in P group will receive a single dose of the placebo solution, as follows: 5 patients will receive 2 mL, 5 patients will receive 3 mL and 5 patients will receive 4 mL.

Immediately after paracetamol or placebo IT administration, all patients will receive a single IT dose of either 12.5 mg (patient's height ≤ 160 cm) or 15 mg (patient's height > 160 cm) Hyperbaric Bupivacaine HCl 0.5%. The time interval between paracetamol IT and bupivacaine 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	60 mg (2 mL)	Hyperbaric bupivacaine HCl 0.5% - Height ≤160 cm: 12.5 mg (2.5 mL) Height >160 cm: 15 mg (3 mL)
D2	15			90 mg (3 mL)	
D3	15			120 mg (4 mL)	
P	15	5	Placebo IT	2 mL	
		5		3 mL	
		5		4 mL	

The investigational product Paracetamol 3% and placebo will be provided in 5-mL ampoules, the non-investigational product Hyperbaric bupivacaine HCl 0.5% will be in 4-mL ampoules (commercial packaging). 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 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

Paracetamol or placebo will be administered intrathecally (IT) just before spinal anaesthesia. Syringes for injection will be prepared inside a curtain cubicle space within the operating room by a person not involved in any other study activity. The syringe preparation area will not be visible from the outside. All the clinical staff (Investigator/co-investigators/study nurses) involved in investigational product administration, anaesthesia, surgery or patient's care will be blind with respect to the administered treatment. Test and 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 for injection and on the transfer of the syringes from the preparation to the operating room will be given in the study manual.

For the intrathecal injection of the analgesic/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 Reganesth or Nizell needle; caudocranial direction of the bevel) 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 in the lateral decubitus position (or sitting, if more appropriate) using a midline approach at the L3/L4 or L4/L5 interspaces. After the lumbar puncture and after verifying the

spontaneous flow of liquor at the beginning and at the end of the procedure, two short aspirations will be done to verify the proper positioning of the needle. Barbotage must be avoided.
After intrathecal administration of the paracetamol dose or placebo, the anaesthetic (Hyperbaric bupivacaine HCl 0.5%) 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 bupivacaine IT administration will be recorded in the case report form (CRF).

Postoperatively all patients will have access to morphine via a PCA device with a standardised programme (1 mg/mL, 1-mg bolus, 5-min lock out time interval, no 4-h dose limit). If adequate pain relief is not achieved with the i.v. PCA device alone, supplemental rescue boluses of i.v. morphine or another analgesic (according to the Investigator's opinion) will be administered as needed, according to standard hospital procedures.

3.1.4 Investigational product distribution

The investigational products and the anaesthetic will be administered by the investigator or by his/her deputy. The person administering the investigational product will also administer the anaesthetic.
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 according to the randomisation list. The primary packaging of the investigational products will be a 5-mL glass ampoule packed in individual carton packages (patients' kits). Each patient kit will contain the glass ampoule with the product and a sealable graduated syringe for the collection of the residual product after administration.

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

Labelling on packages will report:

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

j) The storage conditions.

Labels of the individual syringes of the investigational products (paracetamol/placebo), prepared outside the operating room by a person not involved in any study activity, 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 (Hyperbaric Bupivacaine HCl 0.5%) will be the commercial packaging.

3.3 Storage conditions

The investigational products (Paracetamol and Placebo) and the non-investigational product (Bupivacaine) 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 product will be provided directly to the investigator by the sponsor, in excess of the amount necessary for the study (at least 25% excess).

The non-investigational product will be directly purchased by the clinical centre, 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 study products 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 prospective, single centre, randomised, parallel-group, double-blind, placebo-controlled, three doses of intrathecal paracetamol, exploratory efficacy and safety study

4.2 Discussion of design

The study has been designed to evaluate the effectiveness in reducing postoperative pain of a novel aqueous solution of Paracetamol (Paracetamol Sintetica 3%) administered by intrathecal injection in patients undergoing hip replacement surgery under spinal block.

Administration of paracetamol for postoperative pain management using methods alternative to the traditional oral or i.v. routes is still to be 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 doses of intrathecal Paracetamol 3% investigated in the present study, i.e. 60 mg, 90 mg and 120 mg, 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). The paracetamol doses of the present study are 8 – 17 times lower than the doses normally administered in humans by the oral or i.v. route for post-operative pain control.

The study will be placebo-controlled.
In the study two products (1. paracetamol/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.

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

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 out of the operating room (in a curtain cubicle space) by a person not involved in any other study activity.

Spinal anaesthesia will be performed according to the standard hospital procedures using Hyperbaric Bupivacaine (19). Bupivacaine is a well-known long-acting anaesthetic agent of the amide type for intrathecal (subarachnoid) anaesthesia, commonly used for urological and lower limb surgery lasting 1.5 - 3 hours and for abdominal surgery lasting 1.5 – 2 hours (20).

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

Pre-medication with propofol will be performed in all patients to reduce possible anxiety before the operation. This is common clinical practice.

5 STUDY POPULATION

5.1 Target population

Patients aged 18-80 years, scheduled for hip replacement surgery under spinal anaesthesia with anticipated need for post-operative narcotic analgesia, who have adequate i.v. access and anticipated hospital stay > 48 hours.

5.2 Inclusion criteria

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

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex, age and surgery*: male/female 18-80 years (inclusive) old patients, scheduled for hip replacement surgery, with anticipated need for post-operative narcotic analgesia, adequate i.v. access and anticipated hospital stay > 48 hours.
3. *Body Mass Index (BMI)*: 18 - 34 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

Patients 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. *Pain assessment*: anticipated to be unable to make a reliable self-report of pain intensity
5. *Allergy*: ascertained or presumptive hypersensitivity to the active principles (paracetamol and/or amide type anaesthetics) and/or formulations' ingredients or related drugs, opioids, non-steroidal anti-inflammatory drugs (NSAIDs); history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers could affect the outcome of the study
6. *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 asthma or 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.

7. *Liver function*: Impaired liver function (transaminases > twice upper limit)
8. *Renal function*: Renal dysfunction (creatinine > 2.0 mg/dL)
9. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study, calculated from the first day of the month following the last visit of the previous study
10. *Drug, alcohol*: history of drug or alcohol abuse. Pre-existing dependence on narcotics or known tolerance to opioids
11. *Pregnancy and lactation*: positive pregnancy test at screening, 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)]*
12. *Chronic pain syndromes*: patients with chronic pain syndromes (taking opioids, anticonvulsant agents or chronic analgesic therapy).
13. *Medications*: medication known to interfere with the extent of spinal block for 2 weeks before the start of the study. Paracetamol formulations, other than the investigational product, for 1 week before the start of the study and during the study. Hormonal contraceptives for females are allowed.

5.3.1 Not allowed treatments and other treatments

No medication known to interfere with the extent of spinal block, in particular no therapeutic use of opioids, will be allowed for 2 weeks before the start of the study and during the whole study duration (except for those administered as part of the study).
Paracetamol formulations, other than the investigational product, will not be allowed for 1 week before the start of the study and during the study.
Hormonal contraceptives for females are allowed.

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

After admission to the operating theatre and before the spinal punctures, patients will be pre-medicated with propofol (1-2 mg/kg/h); in addition, an antibiotic will be administered. Ringer's solution will be infused from the beginning of surgery until patient's discharge from the recovery room.

Post-operatively all patients will receive morphine via a PCA device with a standardised programme (1 mg/mL, 1-mg bolus, 5-min lock out time interval, no 4-h dose limit). If adequate pain relief is not achieved with the i.v. PCA device alone, supplemental rescue boluses of i.v. morphine or another analgesic (according to the Investigator's opinion) will be administered as needed, according to the standard hospital procedures.

6 STUDY SCHEDULE

The schedule of the study is summarised at page 12.

6.1 Study visits and procedures

The study protocol foresees a screening visit, one study treatment for each patient, followed by a follow-up phase including an observation period, a final visit and a follow-up. A written informed consent will be obtained before any study assessment or procedure.

The first subject first visit (FSFV) is defined as the 1st visit performed at the clinical centre by the 1st screened 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 IT administration, anaesthesia and surgery
- **Follow-up phase**
  - Visit 3 (Observation period) – from Day 1 after surgery 4 until eligibility for discharge: Efficacy and safety assessments
  - Final visit/early termination visit (ETV) and discharge. In case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV)
  - Day 6±1 (i.e. 5±1 days after analgesic/anaesthetic IT injection and surgery) - Follow-up

	Day	Procedures/Assessments	Notes
Screening - Visit 1	*From day -21 to day -1*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S001, S002, etc.) ➢ Demographic data and life style recording ➢ Previous/concomitant medications ➢ Routine pre-surgery assessments according to the hospital standard procedures, including medical/surgical history, pai history and intensity, physical examination, height, weight, vital signs (blood pressure, heart rate), ECG, SpO_2 ➢ Laboratory tests ➢ Urine pregnancy test for women, if applicable ➢ Inclusion/exclusion criteria evaluation ➢ AE monitoring	
Treatment - Visit 2	*Day 1*	➢ Concomitant medications ➢ Adverse events (before, during and after block placement and surgery) ➢ Inclusion/exclusion criteria evaluation ➢ Subject randomisation ➢ Vital signs, SpO_2 and ECG (if foreseen by the standard hospital procedures) ➢ Baseline pain assessment at rest using a 0-100 mm visual analogue scale (VAS) ➢ Premedication: • Propofol • Antibiotic • Ringer's solution (from surgery start to discharge from recovery room) ➢ Paracetamol intrathecal injection ➢ Anaesthesic intrathecal injection ➢ Surgery	Transfusion monitoring
Follow-up Phase - Observation period – Visit 3	*Day 1 after surgery until eligibility for discharge*	➢ Post-recovery and hospital stay ➢ Concomitant medications ➢ Adverse events, including morphine related adverse events ➢ Blood cell count (Day 2, morning) ➢ Vital signs, SpO_2 and ECG (if foreseen by the standard hospital procedures) ➢ Pain assessment at rest at 1, 2, 3 h and every 3 h up to 48 h after anaesthetic IT injection ➢ Morphine administration by PCA ➢ Total amount of administered morphine recorded at 24 h and 48 h ➢ Additional post-operative analgesia, only if needed, according to the hospital standard procedures ➢ Functional assessment (see § 7.3) ➢ Blocks assessment (see § 7.4)	Transfusion monitoring Standardised meals will be served according to the hospital procedures.

	Day	Procedures/Assessments	Notes
Follow-up Phase - Final Visit/ETV	*At discharge or upon discontinuation for ETV*	➢ Final assessments, including pain assessment at rest (0-100 VAS), before discharge according to the hospital's standard procedures ➢ Aldrete's scoring scale ➢ Vital signs (BP, HR, SpO_2) and ECG (if foreseen by the standard hospital procedures) ➢ Laboratory tests ➢ Concomitant medications ➢ Adverse events, including TNS (questionnaire) ➢ Discharge (when criteria for discharge are met and according to the hospital's standard procedures) In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	
Follow-up Phase - Follow-up	*Day 6±1*	➢ Adverse events, including TNS (questionnaire) ➢ Concomitant medications	

6.2 Diet and lifestyle

Study participants will follow 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 criteria for discharge, according to the hospital procedures.

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

7 DESCRIPTION OF SPECIFIC PROCEDURES

7.1 Physical examination

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

7.1.1 Vital signs

Patients' blood pressure (BP), heart rate (HR) and peripheral oxygen saturation (SpO_2) will be measured by the investigator or his/her deputy after 5 min at rest (sitting position) according to the hospital procedures.
The following normal ranges for haemodynamic variables will be used:

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

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

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

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

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

7.1.2 ECGs

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

The following normal ranges for ECG parameters will be used:

- Heart Rate: 50-90 beats/min

- PR Interval: 100-220 msec
- QRS Duration: ≤ 120 msec
- QT Interval: ≤ 500 msec

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

7.2 Clinical laboratory assays

Samples of blood will be collected. The following laboratory analyses will be performed at screening and before discharge (final visit).

HAEMATOLOGY
Leukocytes, erythrocytes, haemoglobin (conv. units), haemoglobin (IS units), haematocrit, MCV, MCH, MCHC, thrombocytes.

BLOOD CHEMISTRY
Electrolytes: sodium, potassium
Enzymes: alkaline phosphatase, γ-GT, AST, ALT
Substrates/metabolites: creatinine, fasting glucose

At screening, a urine pregnancy test will be performed, if applicable (see § 5.3).

In the morning of the post-operative day (day 2), blood cell count will be repeated.

7.2.1 Transfusion monitoring

If the surgeon/investigator determines that a patient's operation may require a blood transfusion, the transfusion will be performed and monitored according to the standard hospital procedures.
Blood transfusion and transfused blood volume will be recorded in the patient's source documents.

7.2.2 Assessment of treatment-emergent adverse events

7.2.2.1 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 follow-up (day 6±1).

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

Any complication during anaesthesia, e.g. paraesthesia and micturition disorders, will be recorded. Pain at the site of injection will be recorded as adverse event.
Pain at the site of surgery will not be recorded as an adverse event (see § 7.6, 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 signs of systemic (central nervous system) toxicity.

7.2.2.2 Morphine-related adverse events

The following morphine-related adverse events will be carefully monitored:

- Diffuse pruritus,
- Overt respiratory depression requiring treatment,
- Post-operative vomiting or need for anti-emetic medication,
- Sedation, defined as score ≤ -3 on the Richmond Agitation Sedation Scale score (RASS) (23, 24)

A Combined Safety Assessment (defined as the summary of the binary occurrences of any of the events listed above during the first 48 h) will be computed.

7.2.2.3 Transient neurological symptoms

Attention will be given to the possible occurrence of transient neurological symptoms (TNS). In particular the incidence of TNS and unusual sensations not associated to the operation area will be assessed at day 6±1 (i.e. 5±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
- 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

The questionnaire will be reviewed by the investigator who will judge whether the reported symptoms could be classified as TNS on the basis of the available evidence and referring to the diagnosis criteria reported by Pollock *et al.* (25) and ASA, and summarised in the table below:

Table 7.2.2.1 Differential diagnosis criteria for TNS and other events following intrathecal injection

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

7.3 Functional assessment

The following functional assessment parameters, reflecting post-operation recovery status, will be verified:

- Nocturnal awakenings due to pain (number of events, proportion of patients): spontaneously reported by the patient or reported by the patient upon investigator's questioning each morning
- Time to GI motility (return of bowel sounds, flatulence or bowel movement): assessed by the Investigator every 6 h starting from the end of surgery
- Need for postoperative urinary indwelling catheter after initial removal of surgical catheter (proportion of patients)
- Time to resumption of ambulation (from the end of surgery)
- Time to resumption of liquid intake and solid diet (from the end of surgery)
- Time to home discharge (Length of hospital stay) (from the end of surgery)

Results of the assessments will be recorded on the individual CRF.

7.4 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) (15 min when the patient is in the recovery room) and then every 30 min until regression of spinal block and complete regression of sensory block to S1.

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

Readiness for surgery is defined as the presence of an adequate motor block (Bromage's score ≥ 2) and loss of Pinprick sensation. 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 the time when Bromage score returns to 0 and sensitive perception returns to S1), will be reported in the CRF. Start time and end time of surgery will also be recorded.

7.5 Post-operative pain control

7.5.1 Morphine administration

Postoperatively, all patients will have access to morphine via a PCA device with a standardised programme (1 mg/mL, 1-mg bolus, 5-min lock out time interval, no 4-h dose limit).
Time of first morphine use will be recorded.
In the morning of the first postoperative day (24 h post-dose) after completion of the routine nursing activities, the PCA device will be temporarily discontinued and the total amount of morphine administered to the patient recorded. Total amount of administered morphine via the PCA device will also be recorded at 48 h and for the entire study period.
Morphine administration through the PCA device will be disconnected at 48 h after spinal administration only if pain VAS score is ≤30 mm.

7.5.2 Additional post-operative pain control

If adequate pain relief is not achieved with the i.v. PCA device alone, supplemental rescue boluses of i.v. morphine or another analgesic (according to the Investigator's opinion) will be administered as needed, according to standard hospital procedures.

Time when additional analgesia is required will be noted. The analgesic used and its dosage will be recorded in the CRF.

7.6 Pain intensity at rest

Pain intensity at rest, at the site of surgery, will be assessed by the patients using a 0-100 mm visual analogue scale (VAS) at the following time-points:

- Screening, baseline (0 h), 1, 2, 3 h and then every 3 h up to 48 h after anaesthetic IT injection and at discharge.

VAS scores will be measured and reported in the CRF by the Investigator or his/her deputy. The primary efficacy measures will be the VAS scores at each predefined time-point.

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

Table 7.6.1 Recommended tolerance ranges for the scheduled VAS assessment times

VAS assessment times	Tolerance ranges
Screening	Not applicable
Baseline (0 h)	Within 30 min before the anaesthetic IT injection
1, 2, 3 hours after anaesthetic IT injection	± 5 min
6, 9, 12 hours after anaesthetic IT injection	± 10 min
15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 hours after anaesthetic IT injection	± 30 min
Discharge	Not applicable

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

7.7 Procedures for discharge

At the end of the surgical procedure, patients will be moved to the post-operative recovery room, where they will be monitored.

Patients will then be moved from the recovery room to a hospital room when the following criteria are met (internal hospital procedure):

a) Blood pressure and heart rate: ± 20% baseline values
b) SpO_2: > 92%
c) No bleeding
d) No pain (evaluated on a 0-100 mm VAS)
e) No nausea or vomiting

f) Patient must be conscious

Patients typically stay in the hospital for 4-5 days after surgery but this will vary depending on how quickly they progress. Patients will be discharged according to the investigator's opinion and standard hospital procedures. A score ≥ 18 on the modified Aldrete's scoring scale (26; Appendix 18.2) is generally required. Haemodynamic variables must be stable and SpO_2 must be acceptable (> 92%) without oxygen therapy.
Patients will be asked about any adverse events, with particular attention to local toxicity and neurological symptoms, such as paraesthesia of the gluteus and of the lower limb, and to possible allergic reactions (e.g. urticarial). If all the criteria are met and no adverse reactions occur, the patient will be 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

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

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

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

All patients will receive Hyperbaric Bupivacaine HCl 0.5% as spinal anaesthetic before the surgical procedure (§ 3.1.1.3)

8.3 Blinding

This is a double-blind study. Both the Investigator and the patients will not be aware of the treatment administered.

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

- one copy is sent to the manufacturer for the preparation of the individual treatment boxes
- one copy is kept at the CRO Quality Assurance Unit
- one copy is stored in the statistical study 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 procedure) and the CRA/monitor who performs the drug accountability will be aware of the administered treatments.
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 out of the operating room by a person not involved in any other study activity.

8.3.1 Emergency code and unblinding procedures

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

8.3.2 Individual emergency 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 on 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 centres will also receive individual kit replacement envelopes. If a reserve kit needs to be used, the kit replacement envelope will be opened and the injectable solution will be prepared 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 variable

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

Pain at rest VAS scores will be recorded at screening, baseline (0 h), 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 h after anaesthetic IT injection and at discharge, using a 0-100 mm VAS.

9.1.2 Secondary efficacy variables

- Pain at rest VAS scores $AUC_{t1\text{-}t2}$ (0-12h, 12-24h, 24-48h [if applicable] intervals), where $AUC_{t1\text{-}t2}$ is defined as the area under the pain intensity curve at the specified time-intervals
- Total morphine use in the first 24 h, in the first 48 h and in the entire study period
- Time to first morphine use
- Proportion of patients requiring supplementary analgesia, i.e. analgesia other than the planned morphine PCA (i.e. other narcotic or analgesic)
- Time to first supplementary analgesia, i.e. analgesia other than the planned morphine PCA (i.e. other narcotic or analgesic)
- Functional assessment variables (reflecting post-operation recovery status):
  - Nocturnal awakenings due to pain (number of events, proportion of patients)
  - Time to GI motility (every 6 h; return of bowel sounds, flatulence or bowel movement)
  - Need for postoperative urinary indwelling catheter after initial removal of surgical catheter (proportion of patients)
  - Time to resumption of ambulation
  - Time to resumption of liquid intake and solid diet
  - Time to home discharge (Length of hospital stay)
- Morphine-related adverse events:
  - Diffuse pruritus,
  - Overt respiratory depression requiring treatment,
  - Post-operative vomiting or need for anti-emetic medication,
  - Sedation, defined as score ≤ -3 on the Richmond Agitation Sedation Scale (RASS) (see Appendix 18.3)
  - Combined Safety Assessment (defined as the summary of the binary occurrences of any of the events listed above during the first 48 h)
- Time to onset of spinal block (i.e. time to readiness for surgery)
- Maximum level of sensory block
- Time to maximum level of sensory block
- Time to regression of spinal block

9.1.3 Safety variables

- Treatment-emergent adverse events including morphine-related adverse events (see efficacy variables)
- Incidence of transient neurologic symptoms (TNS) at day 6±1 (i.e. 5±1 days after analgesic/anaesthetic IT injection and surgery)
- Vital signs (blood pressure [BP], heart rate [HR] and peripheral oxygen saturation [SpO_2]) and ECG
- Concomitant medications
- Laboratory tests parameters

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 morphine-related TEAEs and to TNS symptoms. Further details on the AE assessments are given in § 7.2.2.

ECG (if foreseen by the standard hospital procedures), blood pressure, heart rate and SpO_2 will be monitored as detailed in § 7.1.1 and 7.1.2.
Occurrence of clinically relevant hypotension or bradycardia will be monitored throughout the study and, if observed, treated according to the hospitals' standard procedures.

Safety laboratory tests will be performed at screening, on the post-operative day (blood cell count) and at final visit according to the standard hospital procedures.
Concomitant medication intake will be recorded.

In addition to the assessments listed above, patients will be monitored for transfusion need, as detailed in § 7.2.1.

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, baseline and background characteristics.
- Full Analysis Set (FAS): all randomised patients who fulfil the study protocol requirements in terms of investigational product (i.e. paracetamol/placebo) and anaesthetic administration and have at least one post-baseline assessment of the primary efficacy evaluation (i.e. pain at rest). This analysis set will be used for 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, anaesthetic administration and primary efficacy evaluation (i.e. 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, FAS, PP set and Safety set).

10.1.2 Reasons for exclusion from the Full Analysis Set

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

- failure to be administered the 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 (15 patients per dose group), aged 18-80 years, scheduled for hip replacement surgery under spinal anaesthesia with anticipated need for post-operative narcotic analgesia, who have adequate i.v. access and anticipated hospital stay > 48 hours will be enrolled in order to have 15 treated patients per treatment group.

The sample size for the study is not based on any formal sample size calculation. The number of 15 treated patients/treatment group 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/evaluation interval (if applicable) and will be summarised by treatment group and assessment time point/evaluation interval (if applicable) using classic descriptive statistics (i.e. mean, SD, CV%, min, median and max) for quantitative variables and tables of frequencies for qualitative variables. Summarisation 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 will be analysed using a 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 (120 mg)
2. P vs. D2 (90 mg)
3. P vs. D1 (60 mg)
4. D1 (60 mg) vs. D3 (120 mg)
5. D2 (90 mg) vs. D3 (120 mg)
6. D1 (60 mg) vs. D2 (90 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

All the analyses on the secondary variables will be performed with a nominal two-sided type I error $\alpha = 0.05$.

The same pairwise comparisons foreseen for the primary variable will be performed.

- Pain at rest will be analysed using a repeated measures ANCOVA with baseline pain at rest as covariate and treatment, assessment time point and treatment*assessment time point as fixed effect.
- Pain at rest VAS scores $AUC_{t1\text{-}t2}$ (0-12h, 12-24h, 24-48h intervals) will be analysed using a rank-transformed ANOVA with treatment as fixed effect. Different analyses will be performed for the $AUC_{t1\text{-}t2}$ (0-12h), $AUC_{t1\text{-}t2}$ (12-24h) and $AUC_{t1\text{-}t2}$ (24-48h).
- Pain at rest VAS scores $AUC_{t1\text{-}t2}$ (0-12h, 12-24h, 24-48h intervals) will be analysed using an ANOVA with treatment as fixed effect. Different analyses will be performed for the $AUC_{t1\text{-}t2}$ (0-12h), $AUC_{t1\text{-}t2}$ (12-24h) and $AUC_{t1\text{-}t2}$ (24-48h)
- Total amount of morphine used in the first 24 h, in the first 48 h and in the entire study period will be analysed using a rank-transformed ANOVA with treatment as fixed effect. Different analyses will be performed for the amount used in the first 24 h, in the first 48 h and in the entire study period.

- Total amount of morphine used in the first 24 h, in the first 48 h and in the entire study period will be analysed using an ANOVA with treatment as fixed effect. Different analyses will be performed for the amount used in the first 24 h, in the first 48 h and in the entire study period.
- Time to first morphine use will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.
- Proportion of patients in need of narcotics other than morphine or in need of other rescue analgesics will be compared between treatment groups by Fisher's exact test.
- Time to first subsequent analgesia (narcotic or NSAIDs) will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.
- Proportion of patients with nocturnal awakenings due to pain will be compared between treatment groups by Fisher's exact test. The same pairwise comparisons foreseen for the primary variable will be performed.
- Number of nocturnal awakenings due to pain will be compared between treatment groups by Wilcoxon rank-sum test.
- Time to GI motility will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.
- Proportion of patients who need postoperative urinary indwelling catheter after initial removal of surgical catheter will be compared between treatment groups by Fisher's exact test.
- Time to resumption of ambulation will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.
- Time to resumption of liquid intake and solid diet will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.
- Time to home discharge will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.
- Proportion of patients with morphine-related adverse events will be compared between treatment groups by Fisher's exact test.
- Time to onset of spinal block will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.
- The maximum level of sensory block will be compared between treatment groups by Wilcoxon rank-sum test.
- Time to maximum level of sensory block will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.
- Time to regression of spinal block will be presented using Kaplan-Meier curves and will be compared between treatment groups by log-rank test.

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 study drug (IMP)
- Other causal relationship
  - Not applicable
  - Relationship to study anaesthetic (NIMP)
  - Relationship to morphine
  - Other

➢ **Morphine-related adverse events**

The occurrence of diffuse pruritus, overt respiratory depression requiring treatment, post-operative vomiting and need for anti-emetic medication or sedation will be summarised by treatment group and overall using tables of frequency.
The scores of the combined safety assessment (0, 1, 2, 3 and 4) will be summarised by treatment group and overall using tables of frequency.

➢ **Physical examination**

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

➢ **Vital signs**

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

➢ **Body weight**

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

➢ **ECG**

Any ECG assessment judged clinical significant will be reported into the CRF.
Date/time of ECG recording, overall investigator's interpretation (as normal, abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) and HR, PR, QRS and QT parameters will be reported in the CRF and listed in the clinical study report. Hard copies of the ECGs will be attached to the CRF. All clinically significant abnormalities after the screening visit will be recorded as AEs.

- **Laboratory data**

Date/time of samples collection and overall investigator's interpretation (N, NCS, CS) will be recorded in the CRF and listed in the final report. Hard copies of the laboratory printouts will be attached to the CRF.
Laboratory data will be inserted into the clinical database and listed in the final report.

- **Incidence of TNS at day 6±1**

The incidence of TNS at day 6±1 (i.e. 5±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 and of morphine will be used.

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

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

11.3 AEs monitoring window

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

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

11.4 AEs recording

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

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

4. End Date/Time: end date/time of the adverse event
5. Affected Body Area: anatomical location relevant for the event
6. Whether the adverse event start before or after the first intake of the study drug or whether the adverse event has worsened or not after the first intake of the study drug
7. Last Study Drug Administration Date/Time Before Onset: if the adverse event started after the first administration of the study drug, the date/time of last administration of the study drug before the onset of the adverse event or
   Last Study Drug Administration Date/Time Before Worsening: In case of treatment emergent adverse event, the date/time of the last administration of the study drug(s) before the worsening of the adverse event.
8. Investigator's opinion about the reasonable possibility of a causal relationship with the study drug.
9. Investigator's opinion about other causal relationship (e.g. non study drug, concomitant therapy, study device, etc.).
10. Severity: the severity or intensity of the event
    - 1 Mild
    - 2 Moderate
    - 3 Severe
11. Pattern: Used to indicate the pattern of the event over time
    - 1 Single Event
    - 2 Continuous
    - 3 Intermittent
12. Serious Adverse Event
13. Action Taken with Study Drug: describes changes to the study drug as a result of the event. It is specifically for actions taken with the study drug
    - 1 Dose Not Changed
    - 2 Dose Increased
    - 3 Dose Reduced
    - 4 Drug Interrupted (i.e. temporary stop)
    - 5 Drug Withdrawn (i.e. definitive stop)
    - 6 Not Applicable (e.g. drug administration not started yet or completed)
    - 7 Unknown
14. Concomitant Therapy: if a concomitant therapy is given, it must be reported in the specific CRF forms
15. Study Discontinuation: if the adverse event cause the subject to be discontinued from the study
16. Other Action Taken: other actions taken as a result of the event that are unrelated to dose adjustments of study drug
17. Outcome: Outcome of the event
    - 1 Recovered/Resolved
    - 2 Recovered/Resolved With Sequelae
    - 3 Recovering/Resolving

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

11.5 SAEs reporting

The investigator must report to the sponsor any SAE within 24 h of becoming aware of the event. The Investigator, within the same timeframe, should also inform the study monitor and the CRO. The investigator shall notify the competent Ethics Committee (EC) within 7 days of any SAE with lethal outcome occurred during a study. If the Investigator is initially unable to obtain all the necessary details for completing the form, he/she should in any case transmit all the available information. The Investigator should provide an appropriate follow-up of SAEs to all concerned parties.
Seriousness and causality must be assessed by the investigator. Expectedness is usually assessed by the sponsor.
If the investigator is unable to assess the causality it is recommended to adopt a conservative approach and treat the event as a suspected adverse reaction until follow-up information is available.
The sponsor may also make an assessment of causality, independent of that of the investigator. The most conservative approach should be taken when it comes to regulatory reporting. Under no circumstances should the sponsor downgrade the investigator's opinion or put the investigator under pressure to change his/her assessment. In case of disagreement, both the opinion of the investigator and the sponsor should be provided 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 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.3/02-2015), 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 § 16.4).

Two monitors will be involved at each centre: one monitor will perform the checks of the study evaluations and procedures and will not be involved in the drug accountability.
A second independent monitor will be defined before the start of the study and will be responsible of 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 unblind 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.

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

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

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

13.2 Quality Control and Quality Assurance

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

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

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

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

13.3 Applicable SOPs

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

13.4 Data access

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

13.5 Audits and inspections

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

14 ETHICAL CONSIDERATIONS

14.1 Ethics and Good Clinical Practice (GCP)

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

The approval of the study protocol by the relevant Ethics Committee and by the Federal Health Authority (Swissmedic) will be obtained before the start of the study.

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

14.2 Informed consent

Before being enrolled 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 regulation and with the requirements of the Health Authorities.

14.4 Withdrawal of subjects

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

14.4.1 Discontinuation type

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

14.4.2 Primary reason for discontinuation

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

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 information leaflet 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 concerned Competent Authority, according to the current regulations in Switzerland.

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

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

15.3 Study documentation and record keeping

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

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

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

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

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

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

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

15.4 Study subjects' recruitment

Study participants will be recruited at the clinical centre among the patients attending the clinic for hip replacement surgery.

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

Data on subjects collected 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.

16 STUDY RESPONSIBLE PERSONS

16.1 Sponsor

Sintetica SA, 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 and coordinating investigator in Switzerland
Claudio Camponovo, MD. Chairman of the Department of Anaesthesiology
Email: ccamponovo@arsmedica.ch

16.3 Clinical laboratory

Synlab Suisse, Via Vira 1, 6942 Savosa, Switzerland
Phone: +41.91.9735620
Fax: +41.91.9711706
Email: info.ticino@synlab.com

Synlab Savosa has an operative laboratory within Clinica Ars Medica, and all analyses will be performed at the clinic.

16.4 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 Reserach S.A., Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
Phone: +41.91.6300510
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Coordination
Angelo Vaccani, Clinical Project Leader
Email: projectmanagement@croalliance.com

Medical Writing Unit Representative
Chiara Leuratti, Medical Writing Manager, 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 TNA questionnaires

CONFIDENTIAL

Study code CRO-15-126
Sponsor code PAR.3/02-2015
Paracetamol IT
Final version 1.0, 01DEC2015

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TRANSIENT NEUROLOGICAL SYMPTOMS
POST-OPERATIVE SURVEY - FINAL VISIT/ETV

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? ☐ Y ☐ N

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 hours after surgery?

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

Pain at the site of surgery? ☐ Y ☐ N

If 0 is no pain and 10 is the worst imaginable pain, how would you rate your average pain at the site of surgery in the hours after 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: _____

CROSS Research S.A. *Page 1*

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Study code CRO-15-126
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TRANSIENT NEUROLOGICAL SYMPTOMS POST-OPERATIVE SURVEY - FOLLOW-UP - DAY 6±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? ☐ Y ☐ N

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 first 5±1 days after surgery?

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

Pain at the site of surgery? ☐ Y ☐ N

If 0 is no pain and 10 is the worst imaginable pain, how would you rate your average pain at the site of surgery in the first 5±1 days after 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: _____

18.2 Modified Aldrete score scale

Hospital_____ Patient number:_____

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

Date:_____ Investigator's Signature:_____

18.3 Richmond Agitation-Sedation Scale

Score	Classification	(RASS)
4	Combative	Overtly combative or violent; immediate danger to staff
3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

From: Sessler CN et al. Am J Resp Crit Care Med. 2002;166(10):1338-1344.
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