CLINICAL STUDY PROTOCOL

Study CRO-16-128 - Sponsor code CHL.3/01-2016

Comparison of epidural Chloroprocaine 3% and Ropivacaine 0.75% for unplanned Caesarean section in labouring women who have an epidural catheter *in situ*

Prospective, multi-centre, randomised, double-blind, controlled, superiority study

EudraCT Number: 2016-000298-20

Test product:	Chloroprocaine HCl 3% Injection (30 mg/mL), Sintetica S.A., Switzerland
Reference product:	Naropin®, Ropivacaine HCl 0.75% injectable solution (7.5 mg/mL), AstraZeneca
Sponsor:	Sintetica S.A., Via Penate 5, CH-6850 Mendrisio, Switzerland Phone: +41.91.640.42.50 Fax: +41.91.646.85.61
International coordinator and Principal investigator site N. 1	Prof. Dr. Marc Van de Velde, MD, PhD, EDRA, Chair Department of Anesthesiology, UZ Leuven, campus Gasthuisberg, Herestraat 49B - 3000 Leuven, Belgium Phone: +32.16.34.1234 Email: marc.vandevelde@uzleuven.be
Development phase:	Phase III
Version and date:	Final version 6.0, 07AUG2020

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

This document comprises 75 pages

VERSIONS' HISTORY

Version	Date	Description of Changes
1.0	17 June 2016	Original submitted document
2.0	03 October 2016	The amended protocol introduces the following changes: If the anesthesia has reached an adequate level with 5 or 10 mL of the investigational anaesthetic and the administration of the additional 10-15 mL give rise to safety concerns, no additional volume will be administered and the patient will be excluded from the study – The Full Analysis set and the Per Protocol set definitions have been slightly modified to exclude from the analyses patients who are withdrawn from the study because not administered the entire volume (20 mL) of study anaesthetic. – The reasons for discontinuation have been completed to include patients discontinued because did not receive the entire planned dose of study anaesthetic (20 mL). – It has been clarified that atropine 0.5 mg will be administered as an i.v. bolus – A few typos were corrected.
3.0	18 October 2017	Both test and reference investigational anaesthetic agents will be administered as 5 mL plus 15 mL over 3 minutes instead of 5 mL plus 5 mL plus 10 mL over 5 minutes. Total volume will be 20 mL as in the previous protocol version. This change has been performed in order to achieve surgical anaesthesia rapidly, taking into consideration the common clinical practice and the medical literature. With the new dose regimen, safety of the study subjects should be increased considering a more rapid and adequate anaesthesia for urgent Caesarean sections. The use of only one test dose as opposed to two test doses as present in the original protocol was balanced against the possible

		delay in establishing the blockade, which in the setting of foetal compromise may not be acceptable. In addition, no published works describe the use of two test doses. The one-5 mL initial dose before the injection of the remaining dose is deemed sufficient also considering that in the study population the epidural catheter has already been tested and used to provide analgesia. In the study, in fact, before undergoing unplanned Caesarean section patients have a continuous infusion of analgesic through a previously placed epidural catheter for CSE analgesia. For a rapid onset of anaesthesia, it is fundamental that the epidural catheter is in place and has been used to maintain labour analgesia until anaesthetic injection. This was not clearly specified in the previous protocol version. Details on the maximal allowed time between end of analgesic infusion and anaesthetic injection have been added. Note to file N. 8 was issued on 08AUG2017 to clarify how to grade the correlation between VAS values for pain assessment and AE severity. The clarification has been added in the current protocol version. Note to file Nr. 4 was issued on 07DEC2016 to clarify that, according to the clinical practice Hetastarch/plasmalyte is used not only at the end but also during surgery. In addition, according to a communication from the Principal Investigator, it has been clarified that according to the clinical practice, Hetastarch and plasmalyte are administered only if needed and their volume cannot be predicted or standardised. The protocol has been amended accordingly. Drug and alcohol abuse will be defined according to the Investigator's opinion on

		the basis of the Dietary Guidelines for Americans 2015-2020, U.S. Department of Health and Human Services and U.S. Department of Agriculture. This information, not present in the previous protocol version, has been added. Non-substantial amendment Nr. 2, dated 06MAR2017, was released and notified to the concerned Health Authorities. With the amendment, the information on the block size of the randomisation list was deleted from the protocol. A new randomisation list starting from patient randomisation number 005 was prepared and used for the study. No information on the block size of the new randomisation list was given in the protocol or in any other document provided to the Investigator and/or the clinical staff. At the time a new version of the protocol was not released. Changes are captured in the present version of the clinical study protocol. Compliance to GCP, ICH Topic E6 (R2) has been introduced. Finally, a few typos found during protocol revision were corrected and a few, minor impact, text modifications were made.
4.0	19SEP19	The amended protocol introduces the following changes: – Three additional centres will participate in the study. The reason is the very low study enrolment rate due to the study inclusion/exclusion criteria, which are particularly restrictive considering the study population, i.e. women in labour undergoing unplanned Caesarean section. – As a consequence of the addition of the three new clinical centres the study design has been changed from single- to multi-centre – This amendment impacts the statistical methodology for the primary and secondary efficacy analysis and the study sample size. The previously

		planned Wilcoxon-rank sum test is in fact not applicable to the analysis of stratified data and needs to be replaced by the Van Elteren test, a widely used extension of the Wilcoxon rank-sum test for non-parametric 2-way analysis. Thus, the sample size was recalculated and the statistical methods for the primary and secondary efficacy outcome analysis were modified accordingly. – The CRO Clinical Project Leader and responsible Biostatistician have changed. – Finally, a few typos found during protocol revision were corrected and a few, minor-impact, text modifications were made.
5.0 (Germany only)	06MAY20	Changes were introduced in the protocol according to the requests of Würzburg Ethics Committee, Germany. The changes were centre-specific and do not have an impact on the other involved sites/countries.
6.0	07AUG2020	The amended protocol introduces the following changes: – In the previous protocol versions 4.0 and 5.0, the sample size was calculated considering a non-competitive design, i.e. each study site was to recruit an equal number of patients. The amended protocol introduces a competitive enrolment, i.e. the sites will be able to enrol an unlimited number of patients until the total number of patients planned for the study has been reached. As a consequence, a new version of the randomisation list (version 5.0), containing the randomisation scheme for patients still to be enrolled at centre 001 and for all patients at centres 002, 003 and 004, will be released. This amendment impacts the statistical methodology for the study sample size calculation and for the primary and secondary efficacy analysis. Thus, the

		sample size was recalculated and the statistical methods for the primary and secondary efficacy outcome analysis were modified accordingly (please refer to the corresponding protocol sections). – Dr. Eva Roofthooft, site N. 2 Principal Investigator (PI), moved from the Department of Anesthesiology, ZNA Middelheim, Antwerpen (Belgium), to Service Anaesthesiology GZA Ziekenhuizen campus Sint-Augustinus, Wilrijk (Belgium). As a consequence site N. 2 name and address have been changed in the protocol. Site N. 2 PI will be Dr. Patrick Van Houwe, whereas Dr. Eva Roofthooft will be the study sub-Investigator. – Site N. 3 PI is Prof. Daniela Marhofer (and not Prof. Oliver Kimberger, as presented in the previous protocol version) – The unique subject identifier has been clarified (par. 12.2). Minor changes were introduced in the paragraph's wording. – Monica Boveri, Senior Clinical Research Associate and Medical Writer, replaced Angelo Vaccani, Senior CPL, for the study coordination. – CTS Clinical Trial Service replaces AML Clinical Services in the blind monitoring of clinical centres N. 1 and 2 starting from AUG2020.

PROTOCOL APPROVAL

SPONSOR
Sintetica S.A., Switzerland

Clinical Project Leader
Elisabetta Donati, Corporate Director Scientific Affairs

14 AUG 2020

Date

Signature

PRINCIPAL INVESTIGATORS

International study coordinator, Principal Investigator and National coordinator - Clinical centre N. 1

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

Prof. Dr. Marc Van de Velde, MD, PhD, EDRA, Chair Department of Anesthesiology, UZ Leuven, Leuven, Belgium

11.08.2020
Date

Signature

PROF. DR. M. VAN DE VELDE
Diensthoofd Anesthesiologie
UZ Leuven
Herestraat 49 - 3000 Leuven
1-07851-13-100

Principal Investigator - Clinical centre N. 2

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

Dr. Patrick Van Houwe, Service Anaesthesiology, GZA Ziekenhuizen campus Sint-Augustinus, Wilrijk, Belgium

17/08/2020
Date

Signature

Dr. P. Van Houwe
Anesthesie
Sint-Augustinus - GZA Ziekenhuizen
1-14652-02-100

Principal Investigator - Clinical centre N. 3

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

Prof. Daniela Marhofer, Priv.-Doz. Dr.med.univ. M.Sc., Orthopedic and Trauma Anesthesia, Medical University of Vienna, Austria

1.9.2020 Daniela Marhofer

Date Signature

CRO for Coordination, Analysis and Reporting
CROSS Research S.A., Switzerland

Coordination
Monica Boveri, Senior Clinical Research Associate and Medical Writer

07 AUG 2020 _____ _____
Date Signature

Medical Writing Team and Clinical Projects Unit Representative
Chiara Leuratti, Clinical Projects Unit Head

18 AUG 2020 _____ _____
Date Signature

Biometry Unit Representative
Alessandra Gentili, Biometry Manager, Unit Head

07 AUG 2020 _____ _____
Date Signature

STUDY SYNOPSIS

Title: Comparison of epidural Chloroprocaine 3% and Ropivacaine 0.75% for unplanned Caesarean section in labouring women who have an epidural catheter *in situ*

Protocol number: CRO-16-128 - Sponsor code CHL.3/01-2016 / EudraCT N. 2016-000298-20

Clinical phase: Phase III

Study design: Prospective, multi-centre, randomised, double-blind, controlled, superiority study

Planned nr. of centres / countries: 4/Belgium, Austria and Germany

International study coordinator and Principal Investigator - site N. 1: Prof. Dr. Marc Van de Velde, MD, PhD, EDRA, Chair Department of Anesthesiology, UZ Leuven, campus Gasthuisberg, Herestraat 49B - 3000 Leuven, Belgium

Investigational product(s):

TEST (T):	Chloroprocaine HCl 3% Injection (30 mg/mL), injectable solution, Sintetica S.A., Switzerland.
REFERENCE (R):	Naropin®, Ropivacaine HCl 0.75% (7.5 mg/mL) injectable solution, AstraZeneca.

Dose regimen: Labouring women who have an epidural catheter *in situ* and established analgesia, in need of an unplanned Caesarean section, will be randomly allocated to receive either Chloroprocaine HCl 3% (T-group) or Ropivacaine HCl 0.75% (R-group) epidurally. Prior to the epidural injection, the patient will be transferred to the operating theatre. The local anaesthetic solution will be freshly prepared and 20 mL will be administered by epidural injection, according to the standard hospitals' procedures, as detailed in the "Study Schedule" section below. *Time T_0 is defined as the start time of the first epidural injection of the investigational product.* In case of pain or discomfort, a 6 mL epidural top-up of the same anaesthetic, i.e. Chloroprocaine HCl 3% in T-group and Ropivacaine HCl 0.75% in R-group, will be administered. The anaesthesiologist(s) administering the anaesthetic and any other staff member collecting study-related data (beside the person preparing the syringes for injection) will be blinded with respect to the treatment given to each patient.

Objective: The objective of this study is to test the superiority in terms of the onset time of anaesthesia and to evaluate the quality of epidural anaesthesia and the safety of Chloroprocaine HCl 3% compared with Ropivacaine HCl 0.75% in patients with an epidural catheter *in situ* undergoing unplanned Caesarean section.

End-points:

Primary efficacy end-point: Time to onset of anaesthesia (i.e. time to reach adequate surgical conditions), defined as time from T_0 to complete loss of cold sensation to the metameric level T4 (block to T4), bilateral

Secondary efficacy end-points:

- Time from T_0 to loss of pinprick and light touch sensation to the metameric level T5 (block to T5), bilateral
- Quality of the block assessed between 10 and 20 min after the end of surgery by the anaesthesiologist and patient together using a 0-10 cm visual analogue scale (VAS; 10=excellent anaesthetic quality, 0=very poor anaesthetic quality)
- Maximum metameric level of the sensory block assessed by three modalities (complete loss of cold, pinprick and light touch sensation)
- Motor block assessment (modified Bromage scale) at baseline, prior to incision and after surgery
- Proportion of patients who need top-up epidural anaesthesia (same anaesthetic as first epidural injection)
- Proportion of patients who need supplementation of the block intraoperatively with intravenous opioids or general anaesthesia
- Proportion of patients who need general anaesthesia

Safety end-points:

- Discomfort and pain assessed during surgery through spontaneous patient's reporting and questioning by the Investigator/anaesthesiologist
- First breakthrough pain assessed by the patient, recorded on a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable)
- Maternal treatment-emergent adverse events, with particular attention to pain (see above), pruritus, nausea, vomiting
- Maternal vital signs, pulse rate, pulse oximetry (SpO_2) and electrocardiogram, monitored from baseline to end of surgery according to the hospitals' standard procedures

STUDY SYNOPSIS (cont.)

Safety end-points, continued:

- Total dose of phenylephrine and total dose of atropine
- Total volume of intravenous fluids
- Neonatal Apgar scores at 1 and 5 minutes
- Umbilical artery and venous blood gases (partial pressure of carbon dioxide [pCO_2], partial pressure of oxygen [pO_2], acidity [pH], base excess [BE]) as an indication of foetal hypoxic stress
- Pain at the site of surgery at final visit/early termination visit, recorded on a 0-10 cm VAS (0=no pain, 10= most severe pain imaginable)
- Pain at the site of epidural injection at final visit/early termination visit, recorded on a 0-10 cm VAS (0=no pain, 10= most severe pain imaginable)
- Concomitant medications
- Neonatal adverse events

Sample size:

To calculate the required study sample size, results from a previous study with Ropivacaine 0.75% (Sanders *et al.*, 2004) were taken into consideration. In this study the mean time to onset of anaesthesia (OA) of Ropivacaine 0.75% was estimated to be approximately 10 minutes. Time to OA was modelled with a positive right-skewed gamma distribution. Assuming an expected difference between Test group and Reference group of μT-μR = -5 minutes (i.e. a decrease from 10 minutes to 5 minutes), and nT = nR, a sample size of 44 subjects in each group will have a power of 90% with a 0.050 two-sided significance level. Sample size was calculated using nGLM.r'. R code (Cundill and Alexander, 2015). Forty-eight (48) subjects per group will be enrolled (for a total of 96 subjects) in order to have at least 44 subjects per group in the Full Analysis Set.

Main criteria for inclusion:

All women requesting epidural analgesia for labour will be evaluated for inclusion in this study once analgesia for labour has been established. When analgesia is effective and if parturients are considered potentially eligible for inclusion according to the criteria below, they will be informed about the study and asked if they would like to participate in the study in the event that an unplanned Caesarean section is required. Written informed consent would then be obtained.

Inclusion criteria:

1. *Informed consent*: Signed written informed consent before inclusion in the study (obtained from women fulfilling the criteria, only when effective analgesia has been established)
2. *Sex, pregnancy status and age*: Labouring women with singleton pregnancy, ≥ 18 years old
3. *Epidural catheter*: Previously sited epidural catheter
4. *ASA physical status*: I-II
5. *Analgesia*: Effective analgesia established following combined spinal epidural analgesia (CSE)
6. *Term gestation*: ≥ 36 weeks
7. *Caesarean section*: Unplanned Caesarean section category 2 or 3, according to Lucas Classification (Lucas et al. J R Soc Med. 2000;93(7):346-50)
8. *Body Mass Index (BMI)*: ≤ 40 kg/m2
9. *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 epidural anaesthesia
2. *ASA physical status:* III-V
3. *Further anaesthesia:* Patients expected to require further anaesthesia
4. *Epidural catheter:* Epidural catheter failure (epidural catheter replacement required or inability to provide effective analgesia)
5. *Pregnancy:* Labouring women with multiple pregnancy
6. *Caesarean section:* Elective Caesarean section
7. *Allergy:* ascertained or presumptive hypersensitivity to the active principle and /or formulations ingredients; ascertained or presumptive hypersensitivity to the amide and ester-type anaesthetics

STUDY SYNOPSIS (cont.)

Exclusion criteria, continued:

8. *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 diseases, eclampsia, antepartum haemorrhage, sepsis, blood coagulation disorders, insulin dependent diabetes mellitus, terminal kidney failure
9. *Medications*: Medication known to interfere with the extent of regional blocks (see chloroprocaine and ropivacaine SmPCs) for 2 weeks before the start of the study.
10. *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
11. *Drug, alcohol*: history of drug or alcohol abuse[1]
12. *Plasma cholinesterase:* Known plasma cholinesterase deficiency

Study schedule:

The study will include a screening phase (Visit 1, day -1 or day 1), a treatment phase (epidural anaesthesia and Caesarean section: Visit 2, day 1), a final visit (after surgery: day 1) and a follow-up (day 3±1).

Screening Phase (Visit 1, day -1 or day 1)

All parturients who receive neuraxial combined spinal-epidural (CSE) labour analgesia will be evaluated for study participation according to the inclusion/exclusion criteria above (except for inclusion criterion N. 7 and exclusion criteria N. 3 and 4, which will be evaluated after the decision to proceed with Caesarean section has been taken).

If considered potentially eligible, patients will receive oral and written study information on the aims, procedures and possible risks of the study and will be asked whether they would like to participate in case of an unplanned Caesarean section. This is done following establishment of effective analgesia BUT prior to the decision to perform a Caesarean section.

When consent is confirmed, a screening number will be assigned to the subjects and the following baseline characteristics will be recorded for all subjects: demography, physical abnormalities, body weight, height, BMI, vital signs, SpO_2, medical/surgical history and previous/concomitant medications. Weeks of gestation will be recorded for all subjects.

If parturients have agreed to participate in the study, but epidural catheter failure is noted during labour analgesia (epidural catheter replacement required or inability to provide effective analgesia), patients will be excluded from further study participation.

If an unplanned Caesarean section is required, inclusion/exclusion criteria, including inclusion criterion N. 7 and exclusion criteria N. 3 and 4, will be confirmed. Eligible patients will be randomly assigned to receive either Ropivacaine HCl 0.75% (R-group) or Chloroprocaine HCl 3% (T-group), according to the assigned randomisation number. The decision to proceed with the Caesarean section will be made by an obstetrician/gynaecologist not involved in the study. Indication for Caesarean section will be recorded.

Treatment Phase (Visit 2, day 1):

The investigational epidural anaesthetic must be administered within 10 minutes of the end of the analgesia. If the time between the end of the previously established analgesia and the start of the anaesthetic epidural injection is > 10 min, the patient will be excluded from the study.

Prior to epidural injection, the patient is transferred to the operating theatre and standard monitoring (electrocardiography, SpO_2 and non-invasive blood pressure and pulse rate) will be applied according to the standard hospitals' procedures. Clinically significant values will be reported as adverse events and treated according to the standard clinical practice. In particular, hypotension (defined as > 10% decrease from baseline systolic pressure) will be treated with 100 µg phenylephrine bolus and bradycardia (defined as heart rate < 50 bpm) with atropine 0.5 mg bolus. Pre-existing CSE analgesia details, i.e. duration of labour-CSE (as hours), pain on a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable), total dose of local analgesic, pre-existing (baseline) level of sensory block (loss of cold sensation only) and motor block (modified Bromage scale [(1=complete motor block (unable to move feet or knees; 2=almost complete block (able to move feet only); 3=partial block (just able to move knees); 4=detectable weakness of hip flexion (between scores 3 and 5); 5=no detectable weakness of hip flexion while supine (full flexion of knees); 6=able to perform partial knee bend)] will be evaluated and recorded.

[1] *Alcohol abuse is defined as use of alcoholic beverages to excess, above moderate drinking. According to the Dietary Guidelines for Americans 2015-2020, U.S. Department of Health and Human Services and U.S. Department of Agriculture, moderate drinking is up to 1 drink/day for women and up to 2 drinks/day for men*

STUDY SYNOPSIS (cont.)

Treatment phase, continued:
Also an aspiration test of the epidural catheter will be performed. No prophylactic i.v. fluid bolus and no prophylactic vasopressor will be administered.
The 20 mL epidural anaesthetic solution will be administered using a standardised approach, according to the standard procedures of the hospitals, as follows: 5 mL of the study anaesthetic solution will be given epidurally (the start of this initial injection is recorded as being T_0) and the sensory block will be assessed after approximately 2 minutes from the first injection using cold, pinprick and touch. Then the remaining 15 mL of the study anaesthetic solution will be administered epidurally. So after 3 minutes from the start of the first epidural injection, the full 20 mL of study anaesthetic solution will have been administered. The administered volume will be recorded in the case report form (CRF). Approximately two minutes after the start of the second injection, the sensory block will be re-assessed using cold, pinprick and touch.
In the event of a patient with a block obtained already after 5 mL and for whom administration of the remaining 15 mL would result in possible safety risks, according to the Investigator's opinion, the patient will not be administered the remaining volume of anaesthetic and will be discontinued from the study.
In case of pain or discomfort, a 6 mL epidural top-up of the same anaesthetic, i.e. Chloroprocaine HCl 3% in T-group and Ropivacaine HCl 0.75% in R-group, will be administered.
The anaesthesiologist(s) administering the anaesthetic and collecting study-related data will be blinded with respect to the treatment given to each patient.
Sensory block will be assessed every 2 min, using cold, pinprick and light touch, as much as possible also during surgery without disturbing the surgical procedure. Sensory block will also be assessed after surgery end. Presence/complete absence of sensation with the three testing modalities (cold, pinprick and light touch) will be recorded. Complete absence of sensation will be scored as 0, presence of sensation will be scored as 1. Time to achieve loss of cold sensation to T4 and loss of touch sensation (pinprick and light touch) to T5 will be recorded. Surgery will start when time to achieve loss of cold sensation to T4 (primary end-point, also defined as time to onset of anaesthesia) is achieved.
Maximum metameric level of the sensory block will be assessed with the three modalities (cold, pinprick, touch) as far as possible without disturbing the surgical procedure.
Motor block will be assessed at baseline, prior to incision and after surgery using the modified Bromage scale.
Any discomfort or pain or any other adverse effects during surgery will be noted. First breakthrough pain will be assessed by the patient using a 0-10 cm VAS and noted. Any pain or discomfort (reported by the patient) during surgery will be treated with 6 mL epidural chloroprocaine 3% (T-group) or 6 mL ropivacaine 0.75% (R-group) as described above. If this measure does not provide adequate analgesia, intravenous opioids or a general anaesthetic will be given according to the Investigator's opinion.
Only if needed, patients will receive intravenously Hetastarch solution (or any other equivalent isotonic/colloidal solution) and/or plasmalyte solution during and/or at the end of the surgery, according to the standard hospitals' procedures. Between 10 and 20 minutes after the end of surgery, the anaesthetist and the patient will assess together the quality of the block using a 10-cm VAS (10=excellent quality, 0=very poor anaesthetic quality).
Patient's characteristics, surgery, obstetric details and the need for fluids will be recorded. Number of patients who need supplementation of the block intraoperatively with intravenous opioids or general anaesthesia and details on the administered analgesic/anaesthetic will be recorded.
Before, during and after surgery, all adverse events will be recorded. Particular attention will be given to the occurrence of pain, pruritus, nausea and vomiting.

Follow-up phase (Final visit, day 1 or early termination visit):
At the end of the surgical procedure, patients will stay in the post-operative recovery room until the criteria for discharge are met according to the hospitals' standard procedures. Maternal vital signs and SpO_2 will be recorded. Pain at the site of injection and pain at the site of surgery will be assessed using a 0-10 cm VAS.
Neonate Apgar scores and umbilical artery and venous blood gases will be recorded. Neonatal AEs will be recorded.
Patients will be asked about any adverse events. If all the criteria are met and no adverse reactions occur, the patient and neonate will be transferred to a hospital room according to the hospital's standard procedures.

Follow-up phase (Follow-up visit): On day 3±1, the investigator or a deputy of the investigator, not aware of the treatment administered, will question the patients about adverse events and in particular any adverse reactions which might have occurred after the final visit, with particular attention to any sign of late systemic toxicity, local toxicity, neurological symptoms (e.g. paraesthesia, motor function problems and pain at the injection site) and allergic reactions. Neonatal adverse events will also be assessed.

STUDY SYNOPSIS (cont.)

Study schedule, continued:

Blinding

Syringes for anaesthetic epidural injection will be prepared by a person not involved in any other study activity and out of the sight of the anaesthesiologist administering the anaesthetic. All the clinical staff (Investigator/co-investigators/study nurses) involved in anaesthesia and study-related data collection will be blind with respect to the administered treatment.

Data recording

Demography and the other baseline data, efficacy and safety data, details on the investigational anaesthetic administered volume and on the surgical procedure (start and end time, comments) will be reported in the individual CRFs.

Data analysis:

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

Definition of analysis sets:

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

Full Analysis set (FAS): all randomised patients who fulfil the study protocol requirements in terms of study anaesthetic administration, i.e. patients who are administered the whole scheduled volume (at least 20 mL) and who are not discontinued due to time between the end of the previously established analgesia and the start of the anaesthetic epidural injection > 10 minutes. Missing values of time to onset of anaesthesia will be replaced with the highest time to onset of anaesthesia detected in the corresponding treatment group. This analysis set will be used for the primary efficacy analysis.

Per Protocol set (PP): all randomised patients who 1) fulfil the study protocol requirements in terms of study anaesthetic administration, i.e. patients who are administered the whole scheduled volume (at least 20 mL, administered as 5 + 15 mL) and for whom time between the end of the previously established analgesia and the start of the anaesthetic epidural injection is ≤ 10 minutes and 2) fulfil the study protocol requirements in terms of primary efficacy evaluation (time to onset of anaesthesia), with no major deviations that could affect the primary efficacy results. This analysis set will be used for sensitivity analysis.

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

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

Efficacy analysis

Gamma Generalized Linear models (GLMs) with clustered robust error will be used to analyse the time to onset of anaesthesia. Marginal means and 95% confidence interval of the difference between the two groups will be reported. Centre will be considered as cluster in the model. The primary analysis will be performed on the FAS and the alpha level will be set at 0.05. A sensitivity analysis will be performed on the PP set keeping the same alpha level of the primary analysis. When applicable and relevant, secondary endpoints will be compared between the two treatment groups using non-parametric tests (Wilcoxon rank-sum test, Chi square test or Fisher exact test) with a nominal alpha level of 0.05. No corrections for multiple testing are considered for the secondary endpoints; hence a strong claim will be possible only for the primary endpoint.

STUDY SCHEDULE

ACTIVITIES	Screening Phase	Treatment Phase	Follow-up Phase	
Visit	**Visit 1 Days -1/1**	**Visit 2 Day 1**	**Final Visit Day 1 or ETV[8]**	**Follow-up Visit Day 3±1**
Informed consent	x			
Demography and lifestyle	x			
Medical/surgical history	x			
Physical examination	x			
Obstetric assessment	x			
Pre-existing CSE analgesia		x		
Previous and concomitant medication	x	x	x	
Height	x			
Body weight, BMI	x			
Maternal vital signs, SpO_2[1]	x	x	x	
Maternal ECG[2]		x		
Inclusion/exclusion criteria	x			
Enrolment and Randomisation	x			
Epidural injection		x		
Unplanned Caesarean section		x		
Sensory block assessment[3]		x		
Motor block assessment[4]		x		
Pain and discomfort assessment		x[5]	x[6]	
Quality of the block[7]			x	
Neonate Apgar score assessment			x	
Umbilical artery and venous blood gas analysis			x	
Patient's adverse events monitoring	x	x	x	x
Neonatal Adverse events assessment			x	x

1. *At screening, final visit/ETV and during the study according to the standard procedures of the hospitals. Clinically significant values will be reported as adverse events and treated according to the clinical practice of the hospitals*
2. *At baseline and up to the end of surgery according to the hospitals' standard procedures. Clinically significant values will be reported as adverse events and treated according to the clinical practice of the hospitals*
3. *The block will be assessed after 2 min from the administration of the first 5 mL epidural anaesthetic bolus. Sensory block will be assessed again after 2 min from the administration of the remaining 15 mL epidural anaesthetic and then every 2 minutes, using cold, pinprick and light touch, as much as possible also during surgery, without disturbing the surgical procedure. Sensory block will also be assessed after surgery end.*
4. *The motor block will be assessed using a modified Bromage scale at baseline, before incision and after surgery*
5. *In general, pain and discomfort will be assessed through spontaneous patient's reporting and Investigator/anaesthesiologist questioning. First breakthrough pain will be evaluated using a 0-10 cm VAS*
6. *At final visit/early termination visit, only pain will be assessed. Pain at the site of injection and pain at the site of surgery will be assessed using a 0-10 cm VAS*
7. *Quality of the block will be assessed by the patient and anaesthesiologist together using a 0-10 cm VAS*
8. *In case of discontinuation, subjects will undergo an early termination visit (ETV)*

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOAC	Attributable-Legible-Contemporaneous-Original-Accurate-Complete
ANOVA	Analysis of Variance
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BP	Blood Pressure
BE	Base excess
BW	Body Weight
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CNSD	Cumulative Normal Standard Distribution
CRF	Case Report Form
CRO	Contract Research Organisation
CRS	Clinical Study Report
CSE	Combined Spinal Epidural analgesia
CSP	Clinical Study Protocol
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
ETV	Early Termination Visit
FAS	Full Analysis Set
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IMP	Investigational Medicinal Product
IV	Intravenous
IVRA	Intravenous Regional Anaesthesia
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
pCO_2	Partial pressure of carbon dioxide
pO2	Partial pressure of oxygen
PP	Per Protocol
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Peripheral oxygen saturation
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
T_{ra}	Time to administration of rescue anaesthesia or rescue analgesia
VAS	Visual Analogue Scale
WHODDE	World Health Organisation Drug Dictionary Enhanced

1 INTRODUCTION

1.1 Background

1.1.1 Epidural anaesthesia in unplanned Caesarean section

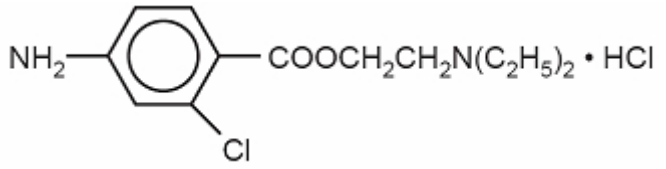
Many patients having planned vaginal delivery will request neuraxial labour analgesia during the course of labour. Unfortunately, a relatively large proportion of patients in labour will require an unplanned Caesarean delivery either due to impaired foetal wellbeing or failed progress of labour. When an epidural catheter is already functional, topping up the epidural catheter to provide good anaesthetic conditions for operative delivery is the option of choice for many anaesthesiologists. So conversion of labour epidural analgesia to anaesthesia for Caesarean section is a common procedure in routine clinical practice. Since unplanned Caesarean delivery can be urgent in order to save the foetus or mother, conversion from analgesia to anaesthesia needs to be reliable and fast, providing effective anaesthetic conditions within minutes from the decision to proceed with surgery.

Various local anaesthetic solutions are available and have been compared in several studies looking at speed of onset of anaesthesia and quality of anaesthesia. A recent meta-analysis of available trials identified two potential epidural top-up solutions as being the most optimal: plain ropivacaine 0.75% or lidocaine 2% with epinephrine and bicarbonate (1). The latter solution works slightly faster but with more breakthrough pain, whilst ropivacaine provided good surgical conditions but with a small delay when compared to the lidocaine solution (2). The disadvantage of the lidocaine solution is that preparation time is required to mix bicarbonate, resulting in potential time-delay between decision to deliver and actual onset of anaesthesia (3). Therefore the standard of practice in the UZ Leuven (study site N.1), is 20 mL epidural ropivacaine 0.75% (25). In the meta-analysis by Hillyard *et al.* (1), chloroprocaine 3% was not evaluated because not yet available in Europe for the proposed indication.

1.1.2 Chloroprocaine

Chloroprocaine hydrochloride (Chloroprocaine HCl [benzoic acid, 4-amino-2-chloro-2-(diethylamino) ethyl ester, monohydrochloride]; Figure 1.1.2.1) is a short-acting local anaesthetic belonging to the amino-ester class, characterized by a rapid onset of action, usually 6 to 12 minutes (5,6), and anaesthesia duration up to 60 min, depending on the amount used and the route of administration. *In-vitro* chloroprocaine half-life is approximately 21-25 seconds.

Figure 1.1.2.1 Chemical structure of chloroprocaine hydrochloride



There is a long history of use of chloroprocaine and the amino ester class of anaesthetics in USA, Canada and Switzerland. Firstly introduced in 1952 (7), chloroprocaine has been

employed as local anaesthetic for decades now, though past episodes of neurological toxicity in patients exposed to spinal anaesthesia with bisulfite-containing chloroprocaine had discouraged a larger use (8-10) It was later demonstrated that neurological complications were associated with the preservative agents added to chloroprocaine formulations (11). As a consequence, preservative-free and also EDTA-free formulations have been developed, and are now available, which prevent these severe adverse episodes and guarantee a safer profile compared to other local anaesthetics (12). Information on chloroprocaine formulations are included in the listed reference drugs SmPCs (Nesacaine® 1%, 2%, 3% for infiltration, peripheral nerve block, epidural block, AstraZeneca [USA and Canada]; Chloroprocaine 1%, 2%, 3% Sintetica SA [Switzerland]; Ivracain® 0.5% Sintetica SA for IVRA [Switzerland]). More recently (2012), Chloroprocaine HCl 1% Injection, preservative-free, Sintetica SA, has received approval for spinal-intrathecal use in several European Countries.
In particular, chloroprocaine 3% solutions have been marketed in USA and Canada for several years and are indicated for the production of local anaesthesia by via the epidural and other administration routes.

The pharmacological properties of chloroprocaine render it unique. Chloroprocaine presents the shortest onset of action and is rapidly metabolized in the circulation by plasma esterase hydrolytic activity. This shortens the duration of action (depending on the amount used and the administration route) and, importantly, prevents the drug's plasma accumulation (5,6) and related risks of toxic systemic spread (5,12-14). Chloroprocaine is used when a fast onset of anaesthesia is necessary and for short-duration surgical procedures (45-60 minutes), when a fast recovery is required (15). There has been a renovated interest for the use of chloroprocaine as local anaesthetic for the epidural block in labouring patients, particularly for patients undergoing an urgent conversion to caesarean section. In this particular setting, chloroprocaine may represent the optimal choice, due to the rapidity of onset and the safest profile for the woman as well as the child (16).

1.2 Rationale

In parturients with an epidural catheter previously placed for labour analgesia, extension of the epidural block is often the preferred option in unplanned Caesarean delivery, provided that adequate speed of onset and adequate surgical anaesthesia are obtained, with minimal side-effects for the mother and the baby. Chloroprocaine has been reported to have a very rapid onset of action and could be an interesting alternative to other anaesthetics currently used for epidural anaesthesia during unplanned Caesarean section.
The objective of the present study is to test the superiority in terms of the onset time of anaesthesia and to evaluate the quality of epidural anaesthesia and the safety of chloroprocaine 3% compared to ropivacaine 0.75% in labouring women with and epidural catheter *in situ* undergoing unplanned Caesarean section.

1.3 Risks and benefits

There are no direct benefits to the patients participating in the study.
Chloroprocaine, however, showed a positive effect on the vascular resistance of the umbilical artery (19), and on the intervillous blood flow during epidural anaesthesia (20).
On the other hand, the short duration of chloroprocaine anaesthesia would require, in some cases, the repetition of the epidural administration. For example with 8 - 10 mL of 2%

chloroprocaine the anaesthesia lasts about 45 - 50 min and the recovery of normal sensitivity is very rapid with pain occurrence.

Local anaesthetics in general cross the placenta, and when used for epidural, paracervical, pudendal or causal block, could cause varying degrees of maternal, foetal and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of anaesthetic used and the technique of drug administration. Adverse reactions in the parturients, fetus and neonate may involve alterations of the central nervous system, peripheral vascular tone and cardiac function (Nesacaine® SmPC).

Epidural anaesthesia with chloroprocaine is widely used during labour, with no untoward effects on the foetal-maternal parameters (16,18).

The risks for the study patients are anticipated to be low, considering that systemic adverse reactions following appropriate use of epidural chloroprocaine are unlikely, due to the small dose absorbed. Chloroprocaine has been on the market under different brand names in USA and Canada for several years. Considering all administration routes, the most commonly encountered acute adverse experiences are related to the central nervous system (CNS) and the cardiovascular system. These adverse experiences are generally dose related and may result from rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anaesthetic solution. In addition to systemic dose related toxicity, unintentional subarachnoid injection of the drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in under-ventilation or apnoea ("Total Spinal"). Factors influencing plasma protein binding, such as acidosis, systemic diseases that alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance. Plasma cholinesterase deficiency may also account for diminished tolerance to ester type local anaesthetics.

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

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

The study design foresees the administration of 20 mL anaesthetic (test or reference) epidurally injected as 5 mL followed by a further 15 mL. There could be cases where the anaesthesia could reach the expected level after one fraction of the planned 20 mL has been

administered. In these cases if the administration of the remaining 15 mL could result in possible safety risks according to the Investigator's opinion, the additional volume will not be administered in order to avoid a too high block and the patient will be discontinued from the study.

Anaesthesia will be carried out in the operating theatre. Monitoring of patient's safety, including peripheral oxygen saturation, will start before anaesthesia and patients will be monitored during the whole procedure.

2 STUDY OBJECTIVES

The objective of this study is to test the superiority in terms of the onset time of anaesthesia and to evaluate the quality of epidural anaesthesia and the safety of Chloroprocaine HCl 3% compared with Ropivacaine HCl 0.75% in patients with an epidural catheter *in situ* undergoing unplanned Caesarean section.

2.1 Primary end-point

The primary study end-point is the time to the onset of anaesthesia (i.e. the time to reach adequate surgical conditions), defined as the time from T_0 (start time of the epidural injection) to complete loss of cold sensation to the metameric level T4 (block to T4), bilateral.

2.2 Secondary end-points

The secondary end-points are:

- Time from T_0 to loss of pinprick and light touch sensation to the metameric level T5 (block to T5), bilateral
- Quality of the block assessed between 10 and 20 min after the end of surgery by the anaesthesiologist and patient together using a 0-10 cm visual analogue scale (VAS; 10=excellent anaesthetic quality, 0=very poor anaesthetic quality)
- Maximum metameric level of the sensory block assessed by three modalities (complete loss of cold, pinprick and light touch sensation)
- Motor block assessment (modified Bromage scale) at baseline, prior to incision and after surgery
- Proportion of patients who need top-up epidural anaesthesia (same anaesthetic as first epidural injection)
- Proportion of patients who need supplementation of the block intraoperatively with intravenous opioids or general anaesthesia
- Proportion of patients who need general anaesthesia

2.3 Safety end-points

- Discomfort and pain assessed during surgery through spontaneous patient's reporting and questioning by the Investigator/anaesthesiologist
- First breakthrough pain assessed by the patient, recorded on a 0-10 cm VAS (0=no pain, 10= most severe pain imaginable)
- Maternal treatment-emergent adverse events, with particular attention to pain (see above), pruritus, nausea, vomiting
- Maternal vital signs, pulse rate, pulse oximetry (SpO_2) and electrocardiogram, monitored from baseline to end of surgery according to the hospitals' standard procedures
- Total dose of phenylephrine and total dose of atropine

- Total volume of intravenous fluids
- Neonate Apgar scores at 1 and 5 minutes
- Umbilical artery and venous blood gases (partial pressure of carbon dioxide [pCO_2], partial pressure of oxygen [pO_2], acidity [pH], base excess [BE]) as an indication of foetal hypoxic stress
- Pain at the site of surgery at final visit/early termination visit, recorded on a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable)
- Pain at the site of epidural injection at final visit/early termination visit, recorded on a 0-10 cm VAS (0=no pain, 10=severe pain)
- Concomitant medications
- Neonatal adverse events

3 CLINICAL SUPPLIES

3.1 Treatment

3.1.1 Description of products

The analytical certificates will be supplied with the investigational medicinal products (IMPs).

3.1.1.1 Test product

TEST (T)

IMP	Chloroprocaine HCl 3% (30 mg/mL), 20 mL vial
Distributor	Sintetica S.A., Switzerland
Manufacturer	Sintetica-Bioren S.A., Switzerland
Pharmaceutical form	Solution for injection
Dose	20 mL (600 mg)
Administration route	Epidural

3.1.1.2 Reference product

REFERENCE (R)

IMP	Naropin® 0.75% (7.5 mg/mL), 20 mL ampoule
Active substance	Ropivacaine HCl
Distributor	AstraZeneca
Pharmaceutical form	Solution for injection
Dose	20 mL (150 mg)
Administration route	Epidural

3.1.2 Dose regimen

Labouring women who have an epidural catheter *in situ* and established analgesia, in need of an unplanned Caesarean section, will be randomly allocated to receive either Chloroprocaine HCl 3% (T-group) or Ropivacaine HCl 0.75% (R-group) epidurally. The local anaesthetic solution will be freshly prepared and the planned volume will be administered by epidural injection, according to the standard hospitals' procedures, as detailed in § 3.1.3 below. Time T_0 is defined as the start time of the epidural injection. In case of pain or discomfort a 6 mL epidural top-up of the same anaesthetic, i.e. Chloroprocaine HCl 3% in T-group and Ropivacaine HCl 0.75% in R-group, will be administered. The anaesthesiologist(s) administering the anaesthetic and any other staff member collecting study-related data (beside the person preparing the syringes for injection) will be blinded with respect to the treatment given to each patient.

3.1.3 Route and method of administration

The decision to proceed with the Caesarean section will be made by an obstetrician/gynaecologist not involved in the study.
The investigational epidural anaesthetic must be administered within 10 minutes of the end of the analgesia. If the time between the end of the previously established analgesia and the start of the anaesthetic epidural injection is > 10 min, the patient will be excluded from the study. Prior to epidural injection, the patient will be transferred to the operating theatre and standard monitoring (electrocardiography, SpO_2 and non-invasive blood pressure and pulse rate) will be applied according to the standard hospitals' procedures. An aspiration test of the epidural catheter will be performed. No prophylactic i.v. fluid bolus and no prophylactic vasopressor will be administered.

The 20 mL epidural anaesthetic solution will be prepared out of sight of the anaesthesiologist (e.g. in a curtain cubicle space) by a person not involved in any other study-related activity will be administered by the anaesthesiologist(s) using a standardised approach, according to the hospitals' standard procedures, as follows: 5 mL of the study anaesthetic solution will be given epidurally (the start of this initial injection is recorded as being T_0) and the block will be assessed after approximately 2 minutes from the first injection using cold, pinprick and touch. Then the remaining 15 mL of the study anaesthetic solution will be administered epidurally. So after 3 minutes from the start of the first epidural injection, the full 20 mL of study anaesthetic solution will have been administered. The administered volume will be recorded in the case report form (CRF).

Approximately, two minutes after the start of the second injection, the sensory block will be re-assessed using cold, pinprick and touch.
In the event of a patient with a block obtained already after 5 mL and for whom administration of the remaining 15 mL would result in possible safety risks, according to the Investigator's opinion, the patient will not be administered the remaining volume of anaesthetic and will be discontinued from the study.

In case of pain or discomfort a 6 mL epidural top-up of the same anaesthetic, i.e. Chloroprocaine HCl 3% in T-group and Ropivacaine HCl 0.75% in R-group, will be administered. The residual amount from the 20 mL vials/ampoules used for the top-up will be collected from each vial/ampoule using another graduated syringe, completely sealable, and retained for drug accountability together with the empty vial/ampoule.

The anaesthesiologist(s) administering the anaesthetic and collecting study-related data will be blinded with respect to the treatment given to each patient. Only if needed, patients will receive intravenously Hetastarch solution (or any other equivalent isotonic/colloidal solution) and/or plasmalyte solution during and/or at the end of the surgery, according to the standard hospitals' procedures.

3.1.4 Investigational product distribution

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

3.2 Packaging and labelling

Each patient's kit will contain two 20 mL-vials/ampoules of either Test (vials) or Reference (ampoules) investigational product. Packaging and labelling will be carried out by the Sponsor according to the randomisation list. Labelling in local language(s) will be applied in such a way that it should not obscure the original label, and 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; 24).

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, prepared at each clinical site out of the sight of the anaesthesiologist by a person not involved in any study activity, will report only the patient's randomisation number. Details will be presented in the study manual.

3.3 Storage conditions

The test product should be stored at 15 - 25°C in a dry locked place, sheltered from light. The reference product should be stored at < 30°C and will not be frozen.
Study kits will be stored at room temperature (15 - 25°C) in a dry locked place, sheltered from light, and will not be frozen.
The storage area will not be accessible to the anaesthesiologist and any other clinical staff involved in study assessments.

3.4 Drug accountability

The test and reference investigational products will be provided directly to the clinical centres by the sponsor, in excess of the amount necessary for the study.

After receipt of the investigational products supply, the pharmacist or the person identified as the recipient of the study drug supply will confirm in writing by signing and dating standard drug accountability forms.

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

4 INVESTIGATIONAL PLAN

4.1 Overall study design

This is a prospective, multi-centre, randomised, double-blind, controlled, superiority study.

4.2 Discussion of design

The study has been designed to evaluate the superiority of chloroprocaine 3% in terms of onset of anaesthesia (i.e. time to reach adequate surgical conditions) after epidural administration, in comparison to ropivacaine 0.75%, in labouring women undergoing unplanned Caesarean section. In designing the study, the following guidelines have been taken into consideration: ICH E9 guideline on Statistical principles for clinical trials (21), ICH E10 guideline on the choice of control groups (22) and EMA guideline "Points to consider on switching between superiority and non-inferiority" (CPMP/EWP/482/99; 23).

A recent meta-analysis of available trials has identified ropivacaine 0.75% or lidocaine 2% with epinephrine and bicarbonate as the two potential most optimal epidural solutions (1). Lidocaine 2% with epinephrine and bicarbonate solution works slightly faster than ropivacaine, with an onset comparable to that of chloroprocaine, but has more breakthrough pain than ropivacaine (2). In addition, the disadvantage of the lidocaine solution is that preparation time is required to mix bicarbonate, resulting in potential time-delay between decision to deliver and actual onset of anaesthesia (3). Therefore the standard of practice in the UZ Leuven is 20 mL epidural ropivacaine 0.75% (4). In the meta-analysis by Hillyard *et al.* (1), chloroprocaine 3% was not evaluated because not yet available in Europe for the proposed indication.

Ropivacaine HCl 0.75% has thus been chosen as the active control based on the above considerations and taking in mind that it is commonly used in Belgium and other European countries for epidural anaesthesia in elective and unplanned Caesarean section (see Naropin® [Ropivacaine HCl] 0.75% SmPC).

It is expected that chloroprocaine will have a shorter time to onset of anaesthesia than ropivacaine. The primary variable has therefore been chosen considering the potential advantage of epidural chloroprocaine in emergency surgical procedures (e.g. unplanned Caesarean section), where a very rapid onset of anaesthesia is essential in order to have an immediate start of the intervention. Chloroprocaine has been previously shown to have a very rapid onset of action, of usually 6-12 minutes, depending on the dose and administration route (see Investigator's Brochure).

According to ICH E9 guideline (21), efficacy will be demonstrated by showing superiority to the active control treatment in terms of the chosen primary variable which can provide a valid and reliable measure of clinically relevant and important treatment benefit in the patient population.

The doses of the Test and Reference anaesthetics have been selected on the basis of the doses of anaesthetics epidurally administered, used in the common clinical practice.

The volume of 20 mL has been chosen on the basis of the paper published by Sanders *et al.* (2) and the standard of practice in UZ Leuven (25).
However, for safety reasons a smaller volume could be administered if an adequate block has been reached with a smaller volume and that the administration of additional anaesthetic could result in safety issues for the patient.

The 20 mL dose of test and reference investigational anaesthetic agents will be administered as 5 mL plus 15 mL over 3 minutes. This dose regimen will be used in order to achieve surgical anaesthesia rapidly, taking into consideration the common clinical practice and the medical literature (1, 26, 27). In this way, a delay in establishing the blockade is reduced, delay that in the setting of foetal compromise may not be acceptable (28). The one-5 mL initial dose before the injection of the remaining dose is deemed sufficient as a test dose, considering that in the study population the epidural catheter has already been tested and used to provide analgesia.

In the study, before undergoing unplanned Caesarean section, patients have a continuous infusion of analgesic through a previously placed epidural catheter for combined spinal-epidural (CSE) analgesia. For a rapid onset of anaesthesia with both Test and Reference products, it is fundamental that the epidural catheter is in place and has been used to maintain labour analgesia until anaesthetic injection (26, 27). In this study, maximal allowed time between end of analgesic infusion and anaesthetic injection is 10 minutes.

Each patient will be allocated to a treatment arm (chloroprocaine or ropivacaine) 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 sight of the anaesthesiologist (e.g. in a curtain cubicle space) by a person not involved in any other study-related activity.

Epidural anaesthesia for unplanned Caesarean section will be performed according to the standard hospitals' procedures.

5 STUDY POPULATION

5.1 Target population

Healthy labouring women (96, in order to have 48 women in each treatment group), aged ≥ 18 years, with an epidural catheter *in situ* undergoing unplanned Caesarean section.

5.2 Inclusion criteria

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

1. *Informed consent*: Signed written informed consent before inclusion in the study (obtained from women fulfilling the criteria, only when effective analgesia has been established)
2. *Sex, pregnancy status and age*: Labouring women with singleton pregnancy, ≥ 18 years old
3. *Epidural catheter*: Previously sited epidural catheter
4. *ASA physical status*: I-II
5. *Analgesia*: Effective analgesia established following combined spinal epidural analgesia (CSE)
6. *Term gestation*: ≥ 36 weeks
7. *Caesarean section*: Unplanned Caesarean section category 2 or 3, according to Lucas Classification (4)
8. *Body Mass Index (BMI)*: ≤ 40 kg/m^2
9. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study.

5.3 Exclusion criteria

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

1. *Physical findings*: Clinically significant abnormal physical findings which could interfere with the objectives of the study. Contraindications to epidural anaesthesia
2. *ASA physical status:* III-V
3. *Further anaesthesia:* Patients expected to require further anaesthesia
4. *Epidural catheter:* Epidural catheter failure (epidural catheter replacement required or inability to provide effective analgesia)
5. *Pregnancy:* Labouring women with multiple pregnancy
6. *Caesarean section:* Elective Caesarean section
7. *Allergy:* ascertained or presumptive hypersensitivity to the active principle and /or formulations ingredients; ascertained or presumptive hypersensitivity to the amide and ester-type anaesthetics

8. *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 diseases, eclampsia, antepartum haemorrhage, sepsis, blood coagulation disorders, insulin dependent diabetes mellitus, terminal kidney failure
9. *Medications*: Medication known to interfere with the extent of regional blocks (see chloroprocaine and ropivacaine SmPCs) for 2 weeks before the start of the study
10. *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
11. *Drug, alcohol*: history of drug or alcohol abuse[2]
12. *Plasma cholinesterase:* Known plasma cholinesterase deficiency.

5.3.1 Not allowed treatments

No medication known to interfere with the extent of spinal block (see chloroprocaine and ropivacaine SmPCs) will be allowed for 2 weeks before the start of the study and during the whole study duration.

5.3.2 Additional anaesthesia

Any discomfort during surgery will be treated with 6 mL epidural chloroprocaine 3% (T-group) or 6 mL ropivacaine 0.75% (R-group). If this measure does not provide adequate analgesia, intravenous opioids or a general anaesthetic will be given, according to the Investigator's opinion.

5.3.3 Premedication/sedation

No prophylactic i.v. fluid bolus and no prophylactic vasopressor will be administered.

5.3.4 Allowed treatments

Phenylephrine 100 µg bolus will be administered to the study subjects in case of hypotension (defined as > 10% decrease from baseline systolic pressure).
Atropine 0.5 mg bolus will be given to the study subjects in case of bradycardia (defined as heart rate < 50 bpm).
Total dose of phenylephrine and total dose of atropine will be decided by the investigator depending on the subject's conditions and will be reported in the CRF.
Only if needed, patients will receive intravenously Hetastarch solution (or any other equivalent isotonic/colloidal solution) and/or plasmalyte solution during and/or at the end of surgery, according to the standard hospitals' procedures.
Allowed concomitant treatments will be reported in the individual CRFs.

[2] *Alcohol abuse is defined as use of alcoholic beverages to excess, above moderate drinking. According to the Dietary Guidelines for Americans 2015-2020, U.S. Department of Health and Human Services and U.S. Department of Agriculture, moderate drinking is up to 1 drink/day for women and up to 2 drinks/day for men*

6 STUDY SCHEDULE

The schedule of the study is summarised at page 17.

6.1 Study visits and procedures

The study protocol foresees a screening visit, 1 study treatment for each patient, followed by final assessment and follow-up. Study duration will be approx. 2-6 days. A written informed consent will be obtained as detailed in § 6.1.1.1 and 14.2.

The first subject first visit (FSFV) is defined as the 1st visit performed by the 1st screened subject. The last subject last visit (LSLV) is defined as the final assessment performed by the last subject, i.e. the last visit foreseen by the study protocol, independently of the fact that the subject is a completer or a withdrawn subject. Additional safety follow-up visits (if needed) may be performed after the LSLV.

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening - visit 1: day -1 / day 1
- **Treatment phase**
  - Visit 2 - day 1: anaesthesia and surgery
- **Follow-up phase**
  - Final visit/early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV)
  - Follow-up visit - day 3±1: Adverse drug reactions check

Details are given below.

6.1.1 Schedule

6.1.1.1 Visit 1 - Screening - Day -1 / Day 1

All parturients who receive neuraxial combined spinal-epidural (CSE) labour analgesia will be evaluated for study participation according to the inclusion/exclusion criteria above (except for inclusion criterion N. 7 and exclusion criteria N. 3 and 4, which will be evaluated at Visit 2 after the decision to proceed with Caesarean section has been taken). If considered potentially eligible, patients will receive oral and written study information on the aims, procedures and possible risks of the study and will be asked whether they would like to participate in case of an unplanned Caesarean section. This is done following establishment of effective analgesia BUT prior to a decision to perform the Caesarean section.
When consent is confirmed, a screening number will be assigned to the subjects and the following baseline characteristics will be recorded for all subjects: demography, physical

abnormalities, body weight, height, BMI, vital signs, SpO_2, medical/surgical history and previous/concomitant medications.

If parturients have agreed to participate in the study, but epidural catheter failure is noted during labour analgesia (epidural catheter replacement required or inability to provide effective analgesia), patients are excluded from further study participation.

If an unplanned Caesarean section is required, inclusion/exclusion criteria, including inclusion criterion N. 7 and exclusion criteria N. 3 and 4, will be confirmed. Eligible patients will be randomly assigned to receive one of the two study anaesthetics (see § 8.1), according to the assigned randomisation number. The decision to proceed with the Caesarean section will be made by an obstetrician/gynaecologist not involved in the study. Indication for Caesarean section will be recorded.

Procedures/Assessments

Before decision to proceed with Caesarean section:

- Obstetric variables
  - weeks of gestation
- Explanation to the subject of study aims, procedures and possible risks when subject's analgesia has been established
- Informed consent signature
- Screening number (as S001, S002, etc.)
- Demographic data
- ASA physical status assessment
- Physical abnormalities
- Body weight, height, BMI
- Medical/surgical history
- Previous/concomitant medications
- Vital signs and SpO_2 (baseline assessment) according to the standard hospitals' procedures
- Inclusion/exclusion criteria evaluation, except for inclusion criterion N. 7 and exclusion criteria N. 3 and 4, which will be evaluated after the decision to proceed with Caesarean section has been taken
- Potential eligibility evaluation

After decision to proceed with Caesarean section has been taken:

- Obstetric variables
  - indication for Caesarean section (4)
- Inclusion/exclusion criteria evaluation, including inclusion criterion N. 7 and exclusion criteria N. 3 and 4
- Eligibility evaluation
- Enrolment and randomisation
- Maternal AEs monitoring

6.1.1.2 Visit 2 - day 1

The investigational epidural anaesthetic must be administered within 10 minutes of the end of the analgesia. If the time between the end of the previously established analgesia and the start of the anaesthetic epidural injection is > 10 min, the patient will be excluded from the study.
Prior to epidural injection, the patient will be transferred to the operating theatre and standard safety monitoring will be applied according to the standard hospitals' procedures (§ 7.3). Baseline pain and the pre-existing (baseline) level of sensory block (loss of cold sensation only) and motor block (Bromage score) will be assessed. Also an aspiration test of the epidural catheter will be performed. No prophylactic i.v. fluid bolus and no prophylactic vasopressor will be administered.

The epidural investigational anaesthetic solution, and the additional 6 mL if needed (see below), will be administered using a standardised approach, according to the standard hospitals' procedures, as described in § 3.1.2 and 3.1.3.
The anaesthesiologist(s) administering the anaesthetic and collecting study-related data will be blinded with respect to the treatment given to each patient.

Sensory block will be assessed as described in § 7.6.1. Surgery will start when time to achieve cold sensation to T4 is achieved.
Motor block will be assessed prior to incision and after surgery using a modified Bromage scale (§ 7.6.2).

Any discomfort or pain or any other adverse effects during surgery will be noted as described in § 7.4. First breakthrough pain will be assessed by the patient using a 0-10 cm VAS and noted. Any discomfort or pain (reported by the patient) during surgery will be treated with 6 mL epidural chloroprocaine 3% (T-group) or 6 mL ropivacaine 0.75% (R-group) If this measure does not provide adequate analgesia, intravenous opioids or a general anaesthetic will be given according to the Investigator's opinion.

Before, during and after surgery, all adverse events will be recorded (§ 7.4). Only if needed, patients will receive intravenously Hetastarch solution (or any other equivalent isotonic/colloidal solution) and/or plasmalyte solution during and/or at the end of the surgery, according to the standard hospitals' procedures.

<u>Procedures/Assessments</u>

- Pre-existing CSE analgesia details
  - duration of labour - CSE (as hours)
  - pain assessed using a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable)
  - total dose of local analgesic used during labour
  - pre-existing (baseline) level of sensory block (loss of cold sensation only) and motor block (Bromage score)
- Epidural anaesthesia administration
- Sensory block assessment (during surgery every 2 min, as much as possible without disturbing the surgical procedure, and after surgery)
- Motor block assessment (before incision and after surgery)

- Standard maternal vital signs, SpO_2 and ECG monitoring, according to the standard hospitals' procedures
- Caesarean section
- Discomfort and pain during surgery
- First breakthrough pain (VAS)
- Maternal AEs with particular attention to pain, pruritus, nausea and vomiting
- Only if needed, iv administration of Hetastarch solution (or any other equivalent isotonic/colloidal solution) and plasmalyte solution according to clinical practice
- Concomitant medications recording, as applicable, particularly intravenous opioids or general anaesthetic (for pain and discomfort during surgery), phenylephrine (for hypotension) and atropine (for bradycardia)

Details on the surgery (if performed, start time, end time and any other relevant information) and need for fluids (if performed, type of administered solution, administration start time, administration end time, administered volume) will be recorded.

6.1.1.3 Final assessments (Final visit, day 1 or early termination visit)

At the end of the surgical procedure, patients will stay in the post-operative recovery room until the criteria for discharge are met according to the hospitals' standard procedures (see § 7.7). The following activities/procedures will be performed:

- Patients moved to post-recovery room (after surgery)
- Maternal vital signs and SpO_2 according to the hospitals' procedures
- Pain at the site of surgery (0-10 cm VAS)
- Pain at the site of epidural injection (0-10 cm VAS)
- Quality of the block assessed between 10 and 20 min after the end of surgery by the anaesthesiologist and patient together (0-10 cm VAS)
- Neonate Apgar scores
- Umbilical artery and venous blood gases
- Maternal AEs, in particular pain (see above), pruritus, nausea and vomiting
- Neonatal AEs
- Concomitant medications
- Transfer to hospital room, if criteria for discharge from the post-operative recovery room are met

6.1.1.4 Follow-up visit (day 3±1)

The investigator or a deputy of the investigator, not aware of the treatment administered, will question the patients about adverse events and in particular any adverse reactions.

<u>Procedures/Assessments</u>

- Maternal and neonatal adverse events, in particular adverse drug reactions
- Concomitant medications

6.2 Diet and lifestyle

On Day 1, patients will be under fasting conditions before surgery. Clear fluids intake is allowed if needed. The patients will remain under fasting conditions according to the investigator's opinion.

7 DESCRIPTION OF SPECIFIC PROCEDURES

7.1 Demography and baseline characteristics

During screening and before/after randomisation, the following data will be recorded:
Before randomisation:

- Demographic variables: age, height, weight, BMI
- Obstetric variables: weeks of gestation, indication for Caesarean section (4)

After randomisation:

- Pre-existing CSE analgesia details:
  - duration of labour - CSE (as hours),
  - pain assessed using a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable),
  - total dose of local analgesic used during labour,
  - pre-existing (baseline) level of sensory block (loss of cold sensation only) and motor block (Bromage score) (see below)

7.2 Physical examination

A physical examination, including evaluation of the physical status according to ASA general relative values, will be performed at the visit 1 (screening visit).

7.3 Standard safety monitoring

Subjects' blood pressure, heart rate and pulse oximetry (SpO2) will be measured and recorded at baseline.

Patient's safety monitoring (electrocardiography, pulse oximetry and non-invasive blood pressure and pulse rate) will be performed from start to end of surgery according to the hospitals' standard procedures.

Clinically significant values will be reported as adverse events and treated according to the standard clinical practice. In particular, hypotension (defined as > 10% decrease from baseline systolic blood pressure) will be treated with 100 µg phenylephrine bolus and bradycardia (defined as heart rate < 50 bpm) with atropine 0.5 mg bolus.

7.4 Assessment of treatment-emergent adverse events

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

Maternal AEs will be assessed throughout the study from the signature of the informed consent up to the final visit/ETV.

Occurrence of clinically relevant hypotension or bradycardia will be monitored throughout the study and, if observed, treated according to the hospitals' standard procedures (see § 7.3).

Particular attention will be given to the occurrence of pain and discomfort during surgery and to the occurrence of pruritus, nausea and vomiting.
Any discomfort or pain or any other adverse effects reported by the patient spontaneously or upon Investigator's soliciting before, during or after surgery, will be noted.

Any discomfort during surgery will be treated with 6 mL epidural chloroprocaine 3% (T-group) or 6 mL ropivacaine 0.75% (R-group). If this measure does not provide adequate analgesia, intravenous opioids or a general anaesthetic will be given, according to the Investigator's opinion.

Maternal systemic and local toxicity symptoms, neurological symptoms and allergic reactions will be monitored throughout the study.

Neonatal AEs, if applicable, will also be recorded and reported in the respective mother CRF.

7.5 Discomfort and pain assessment

Pain assessed during or after surgery through spontaneous patient's reporting and questioning by the Investigator/anaesthesiologist will be reported as adverse event (see § 7.4).

Pre-existing pain, first breakthrough pain, pain at the site of surgery at final visit/early termination visit and pain at the site of epidural injection at final visit/early termination visit will be assessed by the patient using a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable).

The following grading system will be used:

0 cm ≤ VAS ≤ 3 cm	=>	No adverse event
3 cm < VAS ≤ 5 cm	=>	Adverse event with severity 'Mild'
5 cm < VAS ≤ 8 cm	=>	Adverse event with severity 'Moderate'
8 cm < VAS ≤ 10 cm	=>	Adverse event with severity 'Severe'

The verbatim descriptions of the pain adverse events related to the VAS assessment will be consistent with the assessment time points and locations (i.e. pre-existing pain, first breakthrough pain, pain at the site of surgery, pain at the site of injection).

Time of first breakthrough pain will be noted and reported into the CRF.

7.6 Block assessment

7.6.1 Sensory block

The primary outcome measure is the time to onset of anaesthesia, also defined as time to reach adequate surgical conditions.

Onset of anaesthesia, i.e. adequate conditions for surgery, is defined as complete loss of cold sensation to the metameric level T4, bilateral.
As a secondary outcome measure, the time to complete loss of touch sensation (pinprick and light touch) to the metameric level T5, bilateral, will be assessed.

Cold sensation will be verified using an ethyl chloride swab. Touch sensation will be assessed as pinprick touch sensation and light touch sensation using an ethyl chloride swab.

Presence/complete absence of sensation with the three testing modalities (cold, pinprick and light touch) will be recorded. Complete absence of sensation will be scored as 0, presence of sensation will be scored as 1.

The pre-existing (baseline) level of sensory block (loss of cold sensation only) will be assessed and recorded.

The block will be assessed after 2 min from the administration of the first 5 mL epidural anaesthetic bolus. Sensory block will be assessed again after 2 min from the administration of the remaining 15 mL epidural anaesthetic and then every 2 minutes, using cold, pinprick and light touch, as much as possible also during surgery, without disturbing the surgical procedure. Sensory block will also be assessed after surgery end.

Time to complete loss of cold sensation to T4 and to complete loss of touch sensation (pinprick and light touch) to T5 will be calculated from T_0 which is defined as the time of the start of the first epidural anaesthetic injection.

In addition, maximum metameric level of the sensory block will be assessed with the three modalities (cold, pinprick, touch), as far as possible without disturbing the surgical procedure, and recorded in the CRF.

7.6.2 Motor block

Motor block will be assessed at baseline, before Caesarean incision and after surgery, using a modified Bromage scale (1=complete motor block (unable to move feet or knees; 2=almost complete block (able to move feet only); 3=partial block (just able to move knees); 4=detectable weakness of hip flexion (between scores 3 and 5); 5=no detectable weakness of hip flexion while supine (full flexion of knees); 6=able to perform partial knee bend). Motor block scores will be reported in the CRF.

7.6.3 Quality

Quality of the block will be assessed between 10 and 20 min postoperatively by the anaesthesiologist and patient together using a 0-10 cm visual analogue scale (VAS; 10=excellent anaesthetic quality, 0=very poor anaesthetic quality)

7.7 Final assessments

At the end of the surgical procedure, patients will stay in the post-operative recovery room until the criteria for discharge are met according to the hospitals' standard procedures. Vital

signs and SpO_2 will be recorded according to the standard hospitals' procedures. Pain at the site of injection and pain at the site of surgery will be assessed using a 0-10 cm VAS.

Neonatal Apgar scores at 1 and 5 minutes and umbilical artery and venous blood gases (partial pressure of carbon dioxide [pCO_2], partial pressure of oxygen [pO_2], acidity [pH], base excess [BE]) will be recorded.

Patients will be asked about any adverse events. Neonatal adverse events will also be recorded and reported in the respective mother CRF. If all the criteria are met and no adverse reactions occur, the patient and neonate will be transferred to a hospital room according to the hospitals' standard procedures.

7.8 Follow-up assessments

On day 3±1, the investigator or a deputy of the investigator, not aware of the treatment administered, will question the patients about adverse events and in particular any adverse reactions which might have occurred after the final visit, with particular attention to any sign of late systemic toxicity, local toxicity, neurological symptoms (e.g. paraesthesia, motor function problems and pain at the injection site) and allergic reactions. Concomitant medications, if any, will be recorded. Neonatal adverse events will be also assessed.

8 ASSIGNMENT OF STUDY TREATMENT

8.1 Randomisation

The enrolment will be competitive. A block randomization scheme will be created for each centre. A new version of the randomisation list (version 5.0), containing the randomisation scheme for patients still to be enrolled at centre 001 and for all patients of centres 002, 003, and 004, will be released.
The randomisation lists versions 1.0 and 2.0 were related to centre 1 and included patients already enrolled at the time of the amendment, while randomisation lists version 3.0 and 4.0 have been withdrawn.

All the lists were 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) (26). The randomisation lists will be attached to the final clinical study report.

8.2 Treatment allocation

At each clinical centre, patients will be allocated to the Test (Chloroprocaine) arm or Reference (Ropivacaine) arm in a 1:1 ratio according to the applicable study randomisation list and to a competitive enrolment.

Randomisation number will be given to the patients on study day 1 and will be used to allocate each patient to a treatment group, as detailed above. The vials/ampoules with the investigational products will be numbered. Each vial/ampoule will be assigned to the patients according to the corresponding randomisation number.

The randomisation numbers will be 3 digits numbers with the structure [C] [NN], where [C] (0, 2, 3, 4) indicates the centre (0 for centre 001, like all the patients already enrolled at site 001), and [NN] is a unique progressive number within centre (e.g. 001, 002, .., 201, 202,…, 301, 302,…., 401, 402,…).

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 lists were generated and sealed in individual envelopes:

- one copy was 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(s) 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.

At each clinical centre, syringes for injection will be prepared by a person not involved in any other study activity out of the sight of the investigator/anaesthesiologist administering the investigational products. The anaesthesiologist(s) administering the IMP will be under blind conditions and will receive the masked syringe for administration.

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 centres.

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 were sent to the pharmacovigilance representative of the sponsor.
Inside each envelope, the individual randomisation code is clearly indicated, reporting the allocated treatment.

Breaking of an individual randomisation code during the study is allowed only when knowledge of the code is essential for the patient's health. In this case, only the envelope related to the concerned subject will be opened. Individual code breaking will be clearly reported in the patient CRF and on the envelope; the latter is sealed again.
In any case, the monitor must be informed within 24 h from code breaking.

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

8.3.3 Individual kit replacement envelopes

The clinical 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 sight of the investigator/anaesthesiologist administering the investigational products, by a person not involved in any other study activity in such a way that the double-blind condition of the study is maintained. The date and the reason for

opening the kit replacement envelope will be recorded on the envelope and then the envelope will be sealed again.

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

9 EVALUATION PARAMETERS

9.1 Study variables

9.1.1 Primary efficacy variables

- Time to onset of anaesthesia (i.e. time to reach adequate surgical conditions), defined as time from T_0 to complete loss of cold sensation to the metameric level T4 (block to T4), bilateral

9.1.2 Secondary efficacy variables

- Time from T_0 to loss of touch sensation (pinprick and light touch) to the metameric level T5 (block to T5), bilateral
- Quality of the block assessed between 10 and 20 min postoperatively by the anaesthesiologist and patient together using a 0-10 cm visual analogue scale (VAS; 10=excellent anaesthetic quality, 0=very poor anaesthetic quality)
- Maximum metameric level of the sensory block assessed by three modalities (complete loss of cold, pinprick and light touch sensation)
- Motor block assessment (modified Bromage scale) at baseline, prior to incision and after surgery
- Proportion of patients who need top-up epidural anaesthesia (same anaesthetic as first epidural injection)
- Proportion of patients who need supplementation of the block intraoperatively with intravenous opioids or general anaesthesia
- Proportion of patients who need general anaesthesia

9.1.3 Safety variables

- Discomfort and pain assessed during surgery through spontaneous patient's reporting and questioning by the Investigator/anaesthesiologist
- First breakthrough pain assessed by the patient, recorded on a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable)
- Treatment-emergent adverse events, with particular attention to pain (see above, pruritus, nausea, vomiting
- Maternal vital signs, pulse rate, pulse oximetry (SpO_2) and electrocardiogram, monitored from baseline to end of surgery according to the hospitals' standard procedures
- Total dose of phenylephrine and total dose of atropine
- Total volume of intravenous fluids
- Neonatal Apgar scores at 1 and 5 minutes
- Umbilical artery and venous blood gases (partial pressure of carbon dioxide [pCO_2], partial pressure of oxygen [pO_2], acidity [pH], base excess [BE]) as an indication of foetal hypoxic stress
- Pain at the site of surgery at final visit/early termination visit, recorded on a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable)
- Pain at the site of epidural injection at final visit/early termination visit, recorded on a 0-10 cm VAS (0=no pain, 10= most severe pain imaginable)
- Concomitant medications

- Neonatal adverse events.

9.2 Efficacy assessments

9.2.1 Efficacy parameters

Efficacy assessments are based on the primary and secondary efficacy variables listed in § 9.1.1 and 9.1.2 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 the occurrence of pain and discomfort during surgery and also to the occurrence of pruritus, nausea and vomiting. Neonatal adverse events will also be assessed. Further details on the AE assessments are given in § 7.4.

Vital signs, ECG and SpO_2 will be monitored as detailed in § 7.3. Occurrence of clinically relevant hypotension or bradycardia will be monitored throughout the surgical procedure.

Neonatal Apgar scores will be evaluated at 1 and 5 minutes according to the standard hospitals' procedures. Umbilical artery and venous blood gases (partial pressure of carbon dioxide [pCO2], partial pressure of oxygen [pO2], acidity [pH], base excess [BE]) will be assessed, according to the common clinical practice, as an indication of foetal hypoxic stress.

Pain at the site of surgery and pain at the site of epidural injection at final visit/early termination visit, recorded on a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable).

Concomitant medication intake, particularly intravenous opioids or general anaesthetic (for pain and discomfort during surgery), phenylephrine (for hypotension) and atropine (for bradycardia), will be recorded.

10 STATISTICAL METHODS

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

Not available data will be evaluated as "missing values". The statistical analysis will be performed using SAS® system version 9.3 (TS1M1) (26) or higher for Windows (the version will be stated in the final clinical study report).

10.1 Analysis Sets

10.1.1 Definitions

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

A subject will be defined as eligible if she meets all the inclusion/exclusion criteria. Otherwise she will be defined as a screen failure.

A subject will be defined as enrolled in the study if she is included into the treatment phase of the study. The enrolment will be performed through randomised allocation to a treatment arm. A subject will be defined as randomised in the study when she is assigned to a randomised treatment arm.

- Enrolled set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics.
- Full Analysis set (FAS): all randomised patients who fulfil the study protocol requirements in terms of study anaesthetic administration, i.e. patients who are administered the whole scheduled volume (at least 20 mL) and who are not discontinued due to time between the end of the previously established analgesia and the start of the anaesthetic epidural injection > 10 minutes (see § 10.1.2). Missing values of time to onset of anaesthesia will be replaced with the highest time to onset of anaesthesia detected in the corresponding treatment group. This analysis set will be used for the primary efficacy analysis.
- Per Protocol set (PP): all randomised patients who 1) fulfil the study protocol requirements in terms of study anaesthetic administration, i.e. patients who are administered the whole scheduled volume (at least 20 mL, administered as 5 + 15 mL), for whom time between the end of the previously established analgesia and the start of the anaesthetic epidural injection is ≤ 10 minutes (see § 10.1.3) and 2) fulfil the study protocol requirements in terms of primary efficacy evaluation (time to onset of anaesthesia), with no major deviations that could affect the primary efficacy results. This analysis set will be used for sensitivity analysis.
- Safety set: all patients who receive at least one dose of the investigational medicinal product. This analysis set will be used for the safety analyses

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

- discontinuation due to failure to be administered the whole scheduled volume according to the scheduled regimen (at least 20 mL) of the investigational product
- discontinuation due to time between the end of the previously established analgesia and the start of the anaesthetic epidural injection > 10 minutes
- failure to satisfy major inclusion/exclusion criteria (eligibility violations). Subjects who fail to satisfy an inclusion/exclusion criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:
  - the inclusion/exclusion criterion was measured prior to enrolment
  - the detection of the relevant eligibility violations can be made completely objectively
  - all subjects receive equal scrutiny for eligibility violations (blind review)
  - all detected violations of the particular inclusion/exclusion criterion are excluded

10.1.3 Reasons for exclusion from the Per Protocol set

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

- failure to be administered the whole scheduled volume according to the scheduled regimen (at least 20 mL as 5 + 15 mL) of the investigational product
- time between the end of the previously established analgesia and the start of the anaesthetic epidural injection > 10 minutes
- exposure to an investigational product 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

To calculate the required study sample size, results from a previous study with Ropivacaine 0.75% (2) were taken into consideration. In this study the mean time to onset of anaesthesia (OA) of Ropivacaine 0.75% was estimated to be approximately 10 minutes. Time to OA was modelled with a positive right-skewed gamma distribution. Assuming an expected difference between Test group and Reference group of μT-μR = -5 minutes (i.e. a decrease from 10 minutes to 5 minutes), and nT = nR, a sample size of 44 subjects in each group will have a power of 90% with a 0.050 two-sided significance level. Sample size was calculated using nGLM.r'. R code (30).

Forty-eight (48) subjects per group will be enrolled (for a total of 96 subjects) in order to have at least 44 subjects per group in the Full Analysis Set

10.3 Demographic, baseline and background characteristics

Critical demographic characteristics will be examined according to qualitative or quantitative data. Qualitative data (e.g. race) will be summarised in contingency tables. Quantitative data (e.g. body weight, height, BMI) will be summarised using classic descriptive statistics.

10.4 Analysis of efficacy parameters

Gamma Generalized Linear models (GLMs) with clustered robust error will be used to analyse the time to onset of anaesthesia. Marginal means and 95% confidence interval of the difference between the two groups will be reported. Centre will be considered as cluster in the model.

The primary analysis will be performed on the FAS and the alpha level will be set at 0.05.

A sensitivity analysis will be performed on the PP set, keeping the same alpha level of the primary analysis.

When applicable and relevant, secondary endpoints will be compared between the two treatment groups using non-parametric tests (Wilcoxon rank-sum test, Chi square test or Fisher exact test) with a nominal alpha level of 0.05. No corrections for multiple testing are considered for the secondary endpoints; hence a strong claim will be possible only for the primary endpoint.

10.5 Safety and tolerability evaluation

10.5.1 Adverse events

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.

Maternal and neonatal AEs will be listed and summarised in separate listings and tables.

10.5.2 Physical examination

Date of the physical examination, overall investigator's interpretation (as normal [N], abnormal not clinically significant [NCS] or abnormal clinically significant [CS]), clinically significant abnormalities (if any) and the ASA physical status will be reported in the CRF and listed.

10.5.3 Discomfort and pain assessment

Discomfort and pain reported by the patients during the study will be reported as AEs.

First breakthrough pain 0-10 cm VAS values will be listed in the clinical study report and summarised by treatment using descriptive statistics.

Pain at the site of surgery and pain at the site of epidural injection at final visit/early termination visit, recorded on a 0-10 cm VAS (0=no pain, 10=most severe pain imaginable) will be listed in the clinical study report and summarised by treatment using descriptive statistics.

10.5.4 Vital signs and ECG

Clinical significant findings during maternal standard monitoring and any other assessment of vital signs (blood pressure, heart rate, SpO_2) and ECG will be reported in the CRF and listed in the clinical study report. Baseline (screening) and final/early termination values of vital signs (if applicable) will be summarised by descriptive statistics.

10.5.5 Baby assessment

Individual neonatal Apgar scores at 1 and 5 minutes and umbilical artery and venous blood gases (pCO_2, pO_2, pH, BE) will be listed.

10.5.6 Concomitant medication

Individual intake of any medication during the study other than the IMPs will be listed. Particularly, individual total dose of intravenous opioids, general anaesthetic (administered for pain and discomfort during surgery), phenylephrine (administered for hypotension), atropine (administered for bradycardia) and total volume of intravenous fluids will be listed.

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, with a minor deviation due to the present study design. In the study, AEs will be monitored from the confirmation of study enrolment (see § 11.3) and not from the signature of the informed consent, as specified in the SOP.
In addition the CRO SOP does not cover the management of neonatal AEs, which in the present study will be monitored from birth to final assessment (see below) and will be managed as the AEs occurring to study participants, according to CRO SOP. Neonatal AEs, if applicable, will be reported on the corresponding mother CRF and each AE will be reported as being "Maternal" or "Neonatal" in order to allow a correct classification of the AEs.

The full SOP or an operative summary will be made available to the clinical centres.

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)**

Pre-treatment AEs are defined as any AEs 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)**

Treatment-emergent AEs (TEAEs) are defined as any AEs 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) for the Test and the SmPC for the Reference product will be used.

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

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

11.3 AEs monitoring window

Study patient:

- Start of monitoring: from the confirmation of study enrolment (after informed consent signature, decision to proceed with the Caesarean section and confirmation of eligibility)
- End of monitoring: Follow-up

Neonate:

- From after birth until Follow-up

AEs occurring to babies after birth will be reported in the respective mother's CRF as detailed above.

An AE occurring after the final 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 maternal AEs derived by spontaneous, unsolicited reports of the subjects, by observation and by routine open questioning should be collected and reported. In addition, all neonatal AEs derived by observation and by predefined assessments, if applicable, 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 centres) 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. AE type: Maternal or Neonatal

4. Start Date/Time: start date/time of the adverse event or
Follow-up Date/Time: follow-up date/time of the adverse event

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

6. Affected Body Area: anatomical location relevant for the event

7. 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

8. 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.

9. Investigator's opinion about the reasonable possibility of a causal relationship with the study drugs.

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

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

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

13. Serious Adverse Event

14. 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

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

16. Study Discontinuation: if the adverse event cause the subject to be discontinued from the study

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

18. 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 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 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 (defined as day 0).
For fatal and life-threatening SUSARs the EC and Competent Authority (CA) should be informed as soon as possible and in any case within 7 days.

If the initial report is incomplete, e.g. not all the information/assessments were available, a complete report should be sent within an additional 8 days.

SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

The minimum information to be reported includes:

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

11.7 Other events qualified for expedited reporting

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

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

11.8 SAEs: contacts

SAEs must be reported on SAE reporting forms and faxed WITHIN 24 H to the 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/she must also check that the data reported in the CRFs correspond to those in the subject's source documents.
To ensure legibility, the CRFs should be filled out in English, in block capitals with a ball-point pen (not pencil, felt tip or fountain pen). Any correction to the CRFs' entries must be carried out by the investigator or a designated member of staff. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way. A single stroke must be drawn through the original entry. Corrections have to be dated and initialled. In the interest of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full, even if there are no changes from a previous examination. The investigator must provide a reasonable explanation for all missing data.
The CRFs will be completed, signed by the investigator, sent to the CRO Biometry Unit for data management procedures and finally sent to the sponsor.

12.2 Unique subject identifier

All the subjects who sign the informed consent form for the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique subject identifier consists of the sponsor study code (i.e. CHL.3/01-2016), the 3-digit site number (e.g. 001, 002, 003, 004), the 4-digit screening number (e.g. S001, S002, etc.) and, if applicable, the 3-digit subject randomisation number (e.g. 001, 002, etc.). Study code, site 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 randomisation numbers separated by a slash, will appear as subject identifier in the individual listings and figures of the clinical study report..

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 (see § 16.4). Two monitors will be involved at the clinical centres: one monitor will perform the checks of the study evaluations and procedures and will not be involved in the drug accountability.
A second monitor (Sintetica S.A.) 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 unblinded information to blind staff members.

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

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

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

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

13.2 Quality Control and Quality Assurance

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

The clinical sites are 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 requirements.

The CROs 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 centres and the CROs 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 for monitoring activities, audits, IEC review, and regulatory inspections.

13.5 Audits and inspections

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

The study may also be inspected by regulatory authorities.

The investigator and the CRO 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 Health Authority will be obtained before the start of the study. Study notification to the Competent Authorities will be performed according to the current regulations.

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

14.2 Informed consent

Before being enrolled in the clinical study, the subjects must have expressed their consent to participate, after the investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study. In the present study, information to the patients will be given and informed consent will be obtained following establishment of effective analgesia BUT prior to decision to perform a Caesarean section. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language 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/she will confirm, by signing and dating the forms, that informed consent has been obtained.

14.3 Insurance policy

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

14.4 Withdrawal of subjects

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

14.4.1 Discontinuation type

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

14.4.2 Primary reason for discontinuation

- **Adverse event**: Any significant adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 11.2.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication (e.g. administration of an investigational anaesthetic volume smaller than 20 mL)
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **site terminated by sponsor**: an indication that a clinical site was stopped by the study sponsor
- **study terminated by sponsor**: an indication that a clinical study was stopped by its sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason

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

14.4.3 Discontinuation procedures

For any subject discontinuing from data collection only or from interventions and data collection, 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 the administration of the whole anaesthetic injection (at least 20 mL) will not be replaced, whilst subjects discontinued before anaesthetic injection (e.g. due to time between the end of the previously established analgesia and the start of the anaesthetic epidural injection > 10 minutes) or after the first 5 mL anaesthetic injection can be replaced in order to have 40 patients per dose group administered with at least 20 mL.

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 centres

Beside the investigational products, the following study material will be supplied to the clinical centres:

- final version of the study protocol
- CRF for each patient plus some spare copies
- Investigator's Brochure and summary of product characteristic for the test IMP and product information for the reference IMP
- informed consent forms
- individual emergency envelopes
- individual kit replacement envelopes
- study manual
- VAS scales (as applicable)

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 substantial amendments will be sent to the EC and the concerned Competent Authority, as appropriate. The amendment will be applicable only when approved, 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, etc., and the original signed informed consent forms.

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

The investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirements.
These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects, insurance contracts, certificate of analysis of the IMPs, 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 centres among labouring women who have an epidural catheter *in situ* and who, during labour, need an unplanned Caesarean section.

15.5 Confidentiality and data protection

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

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

15.6 Publication policy

The sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the investigator publishing in peer reviewed journals, presenting results at scientific congresses and posting information and results on internet-based public registers and databases.
Study results will be communicated in full to the competent Health Authorities by the submission of a complete clinical study report.

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

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

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
Claudio Camponovo, MD
Department of Anaesthesiology, Clinica Ars Medica,
Via Cantonale, CH-6929 Gravesano, Switzerland
Phone: +41.91.611.6211
Fax: +41.91.605.1559
Email: ccamponovo@arsmedica.ch

16.2 Institutes performing the study

16.2.1 Clinical centres

16.2.1.1 Clinical centre N. 1

Department of Anesthesiology, UZ Leuven, campus Gasthuisberg,
Herestraat 49B - 3000 Leuven, Belgium
Phone: +32.16.34.4270 (Secretary)

International coordinator, Principal Investigator and National Co-ordinator in Belgium
Prof. Dr. Marc Van de Velde, MD, PhD, EDRA
Department of Anesthesiology Chair
Phone: +32.16.34.1234
Email: marc.vandevelde@uzleuven.be

16.2.1.2 Clinical centre N. 2

Service Anaesthesiology, GZA Ziekenhuizen
campus Sint-Augustinus, Oosterveldlaan 24, 2610 Wilrijk, Belgium

Principal Investigator
Dr. Patrick Van Houwe
Phone: +32.3.443.3613 (internal number: 35954)
Email: patrick.vanhouwe@gza.be

16.2.1.3 Clinical centre N. 3

Orthopedic and Trauma Anesthesia, Department of General Anesthesia and Intensive Care Medicine, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria
Phone: +43.1.40400.4100
Fax: +43.1.40400.4028

Principal Investigator and National coordinator in Austria
Prof. Daniela Marhofer, Assoc. Prof. Priv.-Doz. Dr.med.univ. MBA,
Email: daniela.marhofer@meduniwien.ac.at

16.2.1.4 Clinical centre N. 4

Department of Anaesthesia and Critical Care
University Hospitals of Würzburg
Oberdürrbacher Str. 6, 97080 Würzburg, Germany
Phone: +49.931.201.0 (Operator)
Phone: +49.931.201.30309 (Clinical Trials Office)

Principal Investigator and National coordinator in Germany
Prof. Peter Kranke, MD, MBA, Professor of Anaesthesia
Mobile: +49.160.90551174
Email: kranke_p@ukw.de

16.3 Co-ordination, data analysis & reporting

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

Coordination
Monica Boveri, Senior Clinical Research Associate and Medical Writer
Email: projectmanagement@croalliance.com

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

Biometry Unit Representative
Alessandra Gentili, Biometry Manager, Unit Head
Email: statistics@croalliance.com

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

16.4 Monitoring

16.4.1 Blind monitoring

16.4.1.1 Clinical centres N. 1 and 2

CTS Clinical Trial Service
Gronausestraat 98, 7581 CJ Losser, The Netherlands

Monitoring representative
Béate ten Bokum, Manager Clinical Operations & Home Care
Phone: +31(0)53.53.62.220
Fax: +31(0)53.53.82.022
Mobile: +31(0)62.82.48.469
Email: beate.tenbokum@clinicaltrialservice.com

16.4.1.2 Clinical centres N. 3 and 4

Dr. Madjid Djeddi
Ina-Seidel-Str. 3 91126 Schwabach,Germany

Monitoring representative
Dr. Madjid Djeddi, Senior Clinical Research Associate, Quality Assurance
Phone: +49.911.632937.4
Mobile: +49.177.388425.9
Fax: +49.911.632937.6
Email: m-djeddi@outlook.com

16.4.2 Open conditions monitoring

Sintetica SA, via Penate 5, CH-6850 Mendrisio, Switzerland

17 REFERENCES

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