

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20997

MEDICAL REVIEW(S)

**FDA CENTER FOR DRUG EVALUATION AND RESEARCH****DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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REVIEW of CLINICAL DATA

NDA: 20-997	RELATED IND:
SPONSOR:	DARWIN DISCOVERY LTD (PAREXEL)
DRUG:	CHIROCAINE (LEVOBUPIVACAINE) INJ.
PROPOSED INDICATION	SURGICAL ANESTHESIA/ PAIN CONTROL
CLINICAL REVIEWER:	MONICA L. ROBERTS, M.D.
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PROJECT MANAGER:	SUSMITA SAMANTA

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INTRODUCTION

BACKGROUND

Mechanism of Action of Local Anesthetics

Clinical local anesthesia is caused by blockade of the excitation-conduction process in nerves. The onset, depth, and duration of local anesthesia depends on the amount of the anesthetic dose that reaches the site of action and how rapidly it arrives and is removed from the receptor site. Eventually, local anesthetic molecules are distributed throughout all body tissues, but the relative concentration in different tissues varies as a function of vascular perfusion, tissue mass and time.

Local anesthetics have a direct effect on both cardiac muscle and vascular smooth muscle. These agents alter the heart's electrical and mechanical activity. Qualitative differences exist between the various local anesthetics. For example, bupivacaine may produce severe cardiac dysrhythmias, including ventricular fibrillation believed to be secondary to a direct cardiac effect.

Drug History

MARKETED DRUG HISTORY

Bupivacaine (Marcaine®, Abbott; Sensorcaine® Astra) is long acting local anesthetic racemic mixture of the levo- and dextro- enantiomers [S(-)- and R(+)-, respectively], and is widely used both in the U.S. and abroad since the mid-1970's. It is currently approved for the "production of local or regional anesthesia for surgery, for oral surgery procedures, for diagnostic and therapeutic procedures, and for obstetric procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia". It is not recommended for intravenous regional anesthesia, pediatric populations under the age of 12 years or for post-operative pain management. (Physicians Desk Reference, 1998).

The rationale for development of levobupivacaine injection, the S(-)- enantiomer form of bupivacaine, was based upon findings indicating that there is anesthetic stereospecificity of action of the cardiac effects, with the S(-)- enantiomer having significantly less cardiotoxicity and similar potency. The sponsor will attempt to prove these claims.

ADMINISTRATIVE HISTORY

Levobupivacaine has been investigated in both animals and humans outside of the USA for a number of years. The IND # _____ "A Double Blind Randomized Controlled Trial of 0.5% Levobupivacaine Compared to 0.5% Bupivacaine for Epidural Anesthesia in Patients Undergoing Elective Cesarean Section" was submitted to allow the initiation and completion of the Phase III program in the U.S.

It was at this time that the sponsor, Chiroscience, requested that the warning label for bupivacaine concerning the use of 0.75% in obstetric patients not be applied to their product – levobupivacaine. The Division's recommendation to Chiroscience was to prepare for the next meeting of the Advisory Committee, scheduled for January 15, 1997, which would serve as an opportunity for them to present their plan for addressing the cardiac profile of levobupivacaine.

ADVISORY COMMITTEE

Chiroscience requested feedback from the committee on the clinical development plan of levobupivacaine with respect to the following:

1. **Pediatric Use** - will four adequate and well-controlled studies be sufficient to support the claim of efficacy and safety in the pediatric population?
2. **Use with other drugs** - Are our planned studies to conduct a small number of well-controlled clinical trials to evaluate the use of levobupivacaine in combination with morphine, fentanyl, and clonidine, sufficient to support labeling?
3. **Cardiac safety** - If the results of the proposed nonclinical and clinical studies show a relative lack of cardiotoxicity, will the committee concur that the black box warning may not be appropriate.

Below please find the FDA's questions to the committee followed by the committee's recommendations¹:

1. What kind and quality of data would be required to remove the box warning from levobupivacaine ?

Recommendation:

- (a) Safety of levobupivacaine must be demonstrated over several animal models and,
 - (b) Safety of levobupivacaine must be demonstrated in at least one clinical study that demonstrates at least a 25% increase in safety over bupivacaine, as shown by a shift in the toxicokinetic curve (lidocaine controls were also suggested) and,
 - (c) Further definition of the nature of the cardiac arrhythmias seen in levobupivacaine in a human model
 - (d) Comment – bupivacaine use is currently very safe and it maybe difficult to show a clear improvement with levobupivacaine; the demonstration of fewer adverse events (e.g., QRS widening, QT dispersion) is most probable.
2. Can the committee make any recommendations regarding specific studies, patients populations, or treatment setting that need to be studied to evaluate the risk of the drug in its anticipated clinical usage?

Recommendation:

- (a) Initial studies on safety should avoid using patients with history of cardiovascular disease. Studies which include cycling females with high progesterone levels would be preliminary to allowing studies for obstetrical use.
 - (b) Requested that patients younger than 6 months be studied separately from older patients (groups of 2 to 5 years and 6 to 12 years) and that a compaeison of caudal/epidural continuous infusions is necessary to determine the toxicity levels in children. An open label study, with or without pharmacokinetic subsets, is appropriate for the pediatric population.
3. Should levobupivacaine 0.75% be considered for the obstetrical population?

Recommendation: As the sponsor does not intend to include levobupivacaine 0.75% for use in obstetrics in the NDA, this question was not considered

¹ Excerpt from the "Summary Minutes of the Anesthetic and Life Support Drugs Advisory Committee", March 24, 1997. Note: responses to the sponsor's questions to the committee were not present in the above-mentioned document.

ORIGINAL NEW DRUG APPLICATION

The NDA applicant is a non-U.S. company, Darwin Discovery Limited, Cambridge, England. PAREXEL International Corporation, Media Pennsylvania, has submitted the NDA on behalf of Darwin Discovery Limited.

This NDA contains twenty-six (26) clinical trials involving 1406 patients demonstrating both efficacy and safety of levobupivacaine injection for use in obstetrics, central and peripheral nerve blocks, postoperative pain management and pediatrics. In addition, there are seven (7) non-contributing ongoing studies, anesthetic "special analysis" conducted on cardiac measures, (which consisted of two studies), and two studies which were not integrated into the database - they were not available at the time the database was locked for analyses.

The Sponsor contends that the development program presented will show that levobupivacaine has a similar efficacy and safety profile to bupivacaine with less cardiovascular and central nervous system toxicity.

SCOPE AND DESIGN OF THE DEVELOPMENTAL PROGRAM

CHEMISTRY

The sponsor has submitted 9 months of stability data for 12 batches on Levobupivacaine Injection as was agreed upon at a teleconference held on January 15, 1998. The sponsor will submit the remaining data as it becomes available.

ANIMAL PHARMACOLOGY

The recommendation of the pharmacology reviewer is to approve the product on the basis its pharmacology and toxicology profile. The laboratory animal and nonclinical studies performed, " support the reasonable safety of this compound for the proposed use in humans"²

² "Review and Evaluation of Pharmacology and Toxicology Data" by M.A. Goheer, Ph.D, 11/6/98

CLINICAL STUDIES

Description - Clinical Studies

There are twenty-six clinical studies: twenty-two controlled and two uncontrolled. A total of 1370 patients have been enrolled in the controlled trials from 31 study sites. Data from 1348 patients are included in the integrated database. The data from the remaining 22 patients (Study 012105) was not available for data integration, but is considered to be critical to support this application. Study 012105 (Part 1 - Phase I, open-label, non-randomized study and Part 2 - double-blind, randomized, parallel study) examines the cardiovascular effects of levobupivacaine when delivered intravascularly). In addition, the sponsor has ongoing studies that do not contribute data to this application. These include dose-ranging and post-operative pain control studies.

Levobupivacaine has been studied at the following concentrations: 0.0625%, 0.125%, 0.5%, 0.75%. Seventeen (17) studies were conducted in Europe and five (5) studies were conducted in the U.S. There is data from both adult and pediatric populations. The adult studies were similar across all studies, with respect to the following: age > 18 years, ASA I to III, undergoing a procedure for which a local anesthetic was appropriate and gave written consent. Efficacy endpoints were time to onset and duration of block, quality of block, need for rescue medication, and Visual Analog Scale pain scores. Safety assessments included the evaluation of adverse events, laboratory values, vital signs, and cardiovascular measurements. The pediatric post-operative pain management study compared efficacy and safety of ilioinguinal-iliohypogastric block versus no treatment in children age 6 months to 12 years undergoing hernia repair.

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Table 1 SUMMARY OF ALL STUDIES SUBMITTED

STUDY #	STUDY DESIGN	Number Treated [Safety (ITT)]	DOSE (s)	AGE MEAN (Range)	SEX (M,F) RACE (W,B,O)	INDICATION/ ADMINISTRATION	OBJECTIVE
OBSTETRIC STUDIES							
030632	Double-blind, randomized, parallel	67(64)	150 mg 0.5% Levo-bupivacaine; 150 mg 0.5% Bupivacaine	29.6 (18-40)	0/69	Elective C.S./ Epidural Catheter Injection	Efficacy, Maternal and Neonatal Blood Levels
CS-001	Double-blind, randomized, parallel	63(62)	150 mg 0.5% Levo-bupivacaine; 150 mg 0.5% Bupivacaine	33.8 (23-40)	0/63 51, 5, 7	Elective C.S./ Epidural Catheter Injection	Efficacy and Safety, Maternal and Neonatal Blood Levels
030276	Double-blind, randomized, parallel, multi-center	169 (162)	>200 mg 0.25% L-bupivacaine >200 mg 0.25% Bupivacaine	27.3 (18-40)	0/169 160,0,9	Labor Epidural; Catheter Injection	Efficacy, Safety, Kinetics
030433	Double-blind, randomized, 2 limb parallel, sequential allocation	73(73)	0.07-12% L-bupivacaine 0.07-0.11% Bupivacaine	26.4 (16-37)	0/73 68,1,4	Labor Epidural Catheter Injection	Minimum Effective Analgesic Conc.
CENTRAL BLOCK STUDIES							
STUDY #	STUDY DESIGN	Number Treated [Safety (ITT)]	DOSE (s)	AGE MEAN (Range)	SEX (M,F) RACE (W,B,O)	INDICATION/ ADMINISTRATION	OBJECTIVE
006175	Double-blind, randomized, 3 limb parallel, multi-center (2)	96(88)	75 mg 0.5% Levo-bupivacaine; 111.2 mg 0.75% Levo-bupivacaine; 75 mg 0.5% bupivacaine	47.2 (19-80)	31/57 88,0,0	Epidural Anesthesia for Elective Lower Limb Surgery	Safety, Dose Response and Kinetics
CS 005	Double-blind, randomized, parallel	56(56)	150 mg 0.75% Levo-bupivacaine, 150 mg 0.75% Bupivacaine	52.5 (28-80)	24/32 53,1,2	Epidural Anesthesia for Major Elective Abdominal Surgery	Efficacy and Safety
030412	Open label, non-randomized	22(22)	15 mg 0.5% Levo-bupivacaine	50.9 (22-72)	12/10 22,0,0,	Subarachnoid Injection for Lower Limb Surgery	Efficacy and Safety

TABLE 1.0 SUMMARY OF ALL STUDIES SUBMITTED (continued)

CENTRAL BLOCK STUDIES - PAIN MANAGEMENT							
STUDY #	STUDY DESIGN	Number Treated [Safety (ITT)]	DOSE (s)	AGE MEAN (Range)	SEX (M,F) RACE (W,B,O)	INDICATION/ ADMINISTRATION	OBJECTIVE
030475	Double-blind, randomized, parallel, multi-center (3)	98(91)	6 ml/hr 0.0625% Levo-bupivacaine; 6 ml/hr 0.125% Levo-bupivacaine; 6 ml/hr 0.25% Levo-bupivacaine	63.8 (32-80)	51/47 95,0,3	Epidural Infusion Post-op Orthopedic Surgery	Efficacy and Safety
CS 004	Double-blind, randomized, 3 arm parallel, multi-center (2)	68(64)	4-10 ml/hr 0.25% Levo-bupivacaine + 0.005% morphine; 4-10 ml/hr 0.25% Levo-bupivacaine 4-10 ml/hr 0.005% morphine	51.6 (25-79)	20/46 63,1,2	Epidural Infusion Post-op Abdominal Surgery	Efficacy and Safety
CENTRAL BLOCK STUDIES - PAIN MANAGEMENT (continued)							
CS 006	Double-blind, randomized, parallel, multi-center (2)	66(65)	0.125% Levo-bupivacaine with 4 ug/cc Fentanyl; 0.125% Levo-bupivacaine; 4 ug/cc Fentanyl,	66.4 (24-80)	20/46 63,1,2	Patient -Controlled Epidural Infusion for Post-op Orthopedic Surgery	Efficacy
030742	Double-blind, randomized, parallel,	96(90) 328 (210)	6 ml/hr 0.125% Levo-bupivacaine + clonidine, 6 ml/hr 0.125% Levo-bupivacaine, 6 ml/hr clonidine	65.5 (40-80)	32/58 90,0,0	Epidural Infusion Post-Hip Replacement	Efficacy and Safety

TABLE 1.0 SUMMARY OF ALL STUDIES SUBMITTED (continued)

PERIPHERAL BLOCK STUDIES							
STUDY #	STUDY DESIGN	Number Treated [Safety (ITT)]	DOSE (s)	AGE MEAN (Range)	SEX (M,F) RACE (W,B,O)	INDICATION/ ADMINISTRATION	OBJECTIVE
030428	Double-blind, randomized, parallel	66(66)	Up to 150 mg 0.25% Levo-bupivacaine, Up to 150 mg 0.25% bupivacaine	56.9 (30-79)	66/0 66,0,0	Infiltration Anesthesia for Post-Inguinal Hernia Repair	Efficacy, Safety and Pharmacokinetics
030721	Double-blind, randomized, parallel	69(69)	Up to 150 mg 0.25% Levo-bupivacaine, Up to 150 mg 0.25% bupivacaine	58.4 (28-88)	69/0 69,0,0	Infiltration Anesthesia for Post-Inguinal Hernia Repair	Efficacy, Safety and Pharmacokinetics
006154	Double-blind, randomized, parallel, multi-center (2)	75/74	0.25% Levo-bupivacaine, 0.5% Levo-bupivacaine, 0.5% bupivacaine,	54.5 (19-84)	49/27 75,0,1	Brachial Plexus Block for Hand Surgery	Dose Response, Kinetics, Safety
CS 009	Open-label, non-comparative	6	Up to 300 mg 0.5% Levo-bupivacaine	56.7 (37-74)	4/2 6,0,0	Axillary Brachial Plexus Block	Efficacy, Safety and Pharmacokinetics
00543	Double-blind, randomized, parallel, multi-center (3)	50(50)	37.5-112.5 mg 0.75% Levo-bupivacaine, 37.5-112.5 mg 0.75% bupivacaine	73.4 (51-92)	23/27 43,2,5	Peribulbar Block for Ophthalmic Surgery	Efficacy
030737	Double-blind, randomized, parallel,	60(60)	37.5mg 0.75% Levo-bupivacaine, 37.5 mg 0.75% bupivacaine	77.1 (56-90)	20/40 60,0,0	Peribulbar Block for Ophthalmic Surgery	Efficacy and Pharmacokinetics
030700	Double-blind, randomized, parallel,	93(93)	Up to 67.5mg 0.75% Levo-bupivacaine, 2% Lidocaine, Placebo	24.7 (18-41)	29/64 79,0,14	Inferior Alveolar Nerve Block and Infiltration for Post-op Dental Pain	Efficacy and Safety

TABLE 1.0 SUMMARY OF ALL STUDIES SUBMITTED (continued)

PEDIATRIC STUDIES							
STUDY #	STUDY DESIGN	Number Treated [Safety (ITT)]	DOSE (s)	AGE MEAN (Range)	SEX (M,F) RACE (W,B,O)	INDICATION/ ADMINISTRATION	OBJECTIVE
CS 007	Single-blind randomized, parallel	35(35)	1.25 mg/kg 0.5% Levo-bupivacaine, no treatment	5.9 (0.5-12.5)	31/4 31,3,1	Ilioinguinal- Iliohypogastric Nerve block for hemiorrhaphy	Efficacy and Safety
PEDIATRIC STUDIES NOT INCLUDED IN THE DATABASE							
030716	Double-blind, randomized, parallel, multi-center (3)	120	0.0625% Levo-bupivacaine, 0.125% Levo-bupivacaine, 0.0625% Levo-bupivacaine + 1ug/ml Fentanyl, 1 ug/ml Fentanyl	(2-12)	M&F	Continuous Epidural Infusion Post- Urological Surgery	
030590	Double-blind, randomized, parallel, multi-center (2)	66	0.25% Levo-bupivacaine, 0.25% bupivacaine,	(0.5-12)	M&F	Caudal Injection Post Orthopedic and Urological Surgery	
030585	Open-label, non-comparative multi-center (2)	4	0.25% Levo-bupivacaine	1.2 0.7-1.8	4/0 4,0,0	Caudal Injection for Post-Genitourinary Surgery	Efficacy and Safety

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EFFICACY FINDINGS

OVERVIEW OF CLINICAL STUDIES

Twenty-two adequate and well-controlled clinical trials have been submitted to this NDA in support of the sponsor's claim for use in obstetrics, central and peripheral blocks, pain management and in pediatric populations. A total of 1370 patients have been enrolled from 31 study sites. Only data from 1348 patients was available for data integration and therefore is included in the integrated database.

The efficacy studies were all randomized, active-controlled (bupivacaine), parallel group and double blind in design. Across the adult studies, patients were over 18 years of age, ASA I to II and were scheduled for surgery for which the use of a local anesthetic technique was appropriate. Efficacy endpoints were time to onset of block, duration of block, quality of block, need for rescue medication, and pain scores.

Additionally, the efficacy studies included comparisons between levobupivacaine and lidocaine as well as an evaluation of the efficacy of levobupivacaine when co-administered with narcotic analgesics. The product has been studied as an infusion as well as in bolus administration.

SUMMARY OF STUDIES PERTINENT TO EFFICACY:

STUDY # ME0400

PROTOCOL SYNOPSIS:

Title: "A Two Phase, Double Blind Three Way Crossover Study to Compared the Effects of Racemic Bupivacaine and Levobupivacaine on the Spectral Components of the EEG"

Primary Objective: "To compare the effects of racemic bupivacaine and levobupivacaine on the EEG."

Secondary Objective: "To assess the safety and tolerability of racemic bupivacaine and levobupivacaine."

[Item 8, Vol. 1. 50, p. 010]

Study Design:

This is a Phase I study designed to investigate the EEG effects of sub-symptomatic doses of bupivacaine and levobupivacaine at a level approaching the maximum sub-symptomatic dose. It was conducted in two phases, both of which were a double blind, randomized, three-way cross-over design. In phase 1, the volunteers received a single infusion of 40 mg bupivacaine, 40 mg levobupivacaine and placebo as a fixed rate infusion over 10 minutes on 3 separate occasions. Phase 2 was identical to phase 1 with the exception of the dose administered, i.e., 50 mg in phase 2. However, it was carried out only if there were no CNS symptoms during phase 1. The dose of bupivacaine and levobupivacaine was the same dose as that used in a previous study in which 12 male volunteers received either 40 mg bupivacaine or 40 mg levobupivacaine by a 8 minute infusion.

Eligible patients, up to 3 weeks before day 1, will undergo a brief screening phase followed by a 1:1:1 randomization to receive either 40 mg bupivacaine, 40 mg levobupivacaine or placebo in a three-way cross-over fashion by peristaltic pump, on each occasion in phase 1. Fifty milligrams of the dose was added to saline to a total volume of 100ml, 80 ml of which was given over 10 minutes or until the appearance of early CNS symptoms or cardiovascular changes.

Eligible patients were males and females (adequately protected against pregnancy) between 18 and 50 years of age, with normal physical examination and laboratory findings, including EEG, with a body weight within 15% of their ideal body weight range for height. Patients had not participated in any clinical study with an investigational drug within 3 months prior to the start of the study, had no symptoms of a clinically significant illness within 4 weeks prior to screening, were nonsmokers or drug abusers, had not used any prescribed medications in the 2 weeks prior to dosing or over-the-counter medications for 7 days prior to dosing, excluding paracetamol, oral contraceptives or hormone replacement therapy. Patients had no history of CNS disorders.

The EEG (10 channels: F3, F4, C3, C4, P3, P4, T5, T6, O1 and O2 all referred to linked mastoids) and EPG (upper canthus of right eye - lower canthus of right eye) were recorded continuously for 35 minutes (using SCANTM 4.0 and SynAmpsTM) beginning 5 minutes before the start of the infusion using silver-silver chloride cup electrodes. Throughout the recording the subject was seated with eyes closed. The EEG and EOG were monitored for signs of drowsiness and, if observed to be falling asleep, the subject was aroused.

The EEG data were subsequently digitized at a rate of 200 Hz and divided into epochs with a length of 5.12 s. Prior to FET analysis each 5.12-second epoch was inspected visually for the presence of artifacts. Artifact-free epochs of EEG were submitted to power spectrum analysis. The EEG recording was divided into 17 2-minute blocks. The individual power spectra were averaged across epochs within each 2-min block of EEG to produce 17 averaged power spectra.

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The amount of absolute and relative (power expressed as a percentage of total power in the spectrum between 1.170-30.030 Hz) power was calculated for the following frequency bands:

- 1) 1.170 - 3.900Hz (delta)
- 2) 3.900 - 7.995 Hz (theta)
- 3) 7.995 - 10.140Hz (low alpha)
- 4) 10.140 - 13.065 Hz (high alpha)
- 5) 13.065 - 20.085 Hz (low beta)
- 6) 20.085 - 30.030 Hz (high beta)
- 7) 1.170 - 30.030Hz (total power - absolute power only).

STATISTICAL ANALYSIS

"The analysis of the data was performed on all subjects who received the study medication. The time of maximal effect (t_{max}) magnitude of maximal effect (E_{max}) and area under the effect-time curve (AUC) were determined for total EEG power, absolute and relative power in the delta, theta, low alpha, high alpha, low beta and high beta bands at each electrode and the ratio of power in high (beta and high alpha): low (low beta, theta and delta) frequencies. E_{max} and AUC were analysed by analysis of variance with the following factors: subject, period, sequence and treatment. Sequence was tested against subject (sequence). Contrasts and 95% confidence intervals were computed for all statistically significant global treatment effects. t_{max} was analysed using Wilcoxon's Matched Pairs Ranked Sum Test.

The time-profiles of the EEG effects were analysed by repeated measures analysis of variance on total EEG power, absolute and relative power in the delta, theta, low alpha, high alpha, low beta and high beta bands and ratio high:low frequency power at each electrode.

$p < 0.05$ was used as the critical alpha level in statistical analysis. The alpha level was not adjusted for multiple comparisons, due to the exploratory nature of this study, as this leads to inflation of type II errors. Therefore, approximately 5% (3) of significant differences may have occurred by chance."

[Item 8, Vol. 1.50, p. 023]

PROTOCOL AMENDMENT:

Amendment 1 dated 7/25/97 and Amendment 2 dated 8/27/97 made the following changes:

- A. Total Power in the Spectrum
- Has been changed from 1.30Hz to 1.170-30.030 Hz
- B. Data Analysis
- The word "baseline-corrected" from the following phrase: "The time of maximal effect (t_{max}) magnitude of maximal effect (E_{max}) and area under the EEG change-time curve (AUC) will be determined for *baseline-corrected* total EEG power and *baseline-corrected* absolute and relative power in the delta, theta, low alpha, high alpha, low beta and high beta bands at each electrode position and mean systolic, diastolic, mean arterial pressure and heart rate."
 - The time-profile of the ECG will now be analyzed by repeated measures analysis of variance on each parameter, in addition to the EEG and blood pressure effects.
- C. Statistical Analysis
- "Absolute and relative EEG power in each frequency band and at each electrode position will be corrected for baseline by calculating the change in EEG power relative to 2 min of EEG prior to start of the infusion" will be deleted.
 - The following phrase will be amended to include the italicized wording, as follows:
"The time-profile of the EEG effect, blood pressure parameters *and QRS duration (up to 4 hours post-dose)* will be analysed by repeated measures analysis of variance on total EEG power and absolute and relative power in the delta, theta, low alpha, high alpha, low beta, and high beta bands at each electrode position and mean systolic, diastolic, mean arterial pressure, heart rate and QRS duration."
 - The following phrase will be inserted: "An analysis of the 12-lead EKGs will be done for QT dispersion, but this analysis will be the subject of a separate protocol."

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CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 12 volunteers randomized, 11 (92%) received study medication and were considered to be evaluable for the safety analyses. One of the 12 volunteers randomized, one withdrew prior to study drug administration, due to an inability to cannulate. Volunteer 009 was withdrawn after receiving 30 mg of levobupivacaine during phase 1 secondary to complaints of "facial tingling". The data from this session was analyzed in the same way as those who had received a full 10 minute (40 mg) infusion.

Protocol Deviations

On three occasions EKGs were not recorded at 10 minutes post infusion and on 4 further occasions vector loops were not recorded for EKGs at 10 minutes post infusion. On each of these occasions, data was not recorded.

[Item 8, Vol. 1.50, p. 025]

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Demographics

A total of 12 subjects, 5 male and 7 female, were enrolled. Their mean age of 32 years (range 20-50 years, SD = 10). The mean height was 169 cm (SD=10) and a mean weight of 70 kg (SD=9 kg). The most commonly reported medical condition was myopia (50%) allergies (33%) and gastrointestinal disorders (25%). Two patients reported a psychiatric history -anxiety and exam stress- both were of these histories were considered not to be of clinical significance.

A total of 4 volunteers took medication within 2 weeks prior to the start of the study – contraception. Paracetamol and Loperamide were taken during the course of the clinical trial.

SPONSOR'S EFFICACY RESULTS:

EEG data was not recorded from subject 005 during session 3 (placebo) because the patient was withdrawn prior to dosing. Additionally, spectral parameters could not be derived for the timepoints listed in the sponsor's table below secondary to the presence of multiple artifacts presumed to be electrical interference, i.e., they appeared after the start of the infusion and disappeared at the end of the infusion.

Table 2. Timepoints for which Spectral Parameters Could Not be Derived
(adapted from sponsor's table III)

SUBJECT	PERIOD	TREATMENT	TIMEPOINTS [time (min) from start of infusion]
004	2	Placebo	2-4, 4-6, 6-8
004	3	Levobupivacaine	2-4, 4-6, 6-8, 8-10
008	2	Placebo	2-4, 4-6, 6-8, 8-10
011	3	Levobupivacaine	4-6

[Item 8, Vol. 1.50, p. 031]

“Due to levobupivacaine and bupivacaine tending to decrease high alpha, low beta, high beta and the ratio of high:low frequencies, minimum values of these parameters were taken as maximal effect. AUCs were calculated according to the linear trapezoidal rule. Values of E_{max} and AUC were transformed ($\ln(x)$) prior to analysis in order to comply with the assumptions of analysis of variance.

Bupivacaine increased AUC for theta power at P4 (absolute power) and C4 (relative power) and decreased AUC for absolute high alpha power at C4 and relative high alpha power at F3, C3, C4, P3, P4, T5, T6, O1. Bupivacaine reduced AUC for ratio of high:low frequencies at P3, P4, T5, T6, O1 and O2.

Levobupivacaine decreased AUC of relative high alpha power and ratio of high:low frequencies to a lesser extent than bupivacaine: relative power in the high alpha band was decreased at T5, T6 and O1 only and ratio of high:low power was decreased at P4 and T6 only. Furthermore, the decrease in relative high alpha power at T5, T6 and O1 and the decrease in ratio of high:low frequencies at P4 were significantly less than those after bupivacaine.

Analysis of variance performed on E_{max} revealed that bupivacaine increased absolute theta in the parietal electrodes (P3 and P4), decreased relative high alpha power at C3 and at the posterior electrodes (P3, P4, T5, T6, O1 and O2) and decreased the ratio of high:low frequencies at P3, P4 and O2.

Levobupivacaine decreased E_{max} of relative high alpha power at P3, P4, T5, T6, O1 and O2, however, the effect of levobupivacaine was significantly less than that of bupivacaine at the parietal electrodes. The E_{max} of the ratio of high:low frequencies at P3, P4 and O2 was reduced following levobupivacaine but to a lesser extent than bupivacaine at P3. Levobupivacaine did not produce a significant increase in the E_{max} of theta power.

Comparison of t_{max} between treatments by the Wilcoxon Rank Sums test revealed a significant effect at C4 for relative high alpha ($p=0.283$) and relative high beta ($p=0.0398$).

Prior to analysis, the recommended transformations ($\ln(x)$ for absolute power and $\ln(x/1-x)$ for relative power) were applied to the EEG data (see Gasser et al, 1982 and John et al, 1980) to comply with the assumptions of analysis of variance.

Bupivacaine increased theta power at T5 (absolute power) and P4 (relative power) and produced a decrease in high alpha power which was statistically significant at all electrode positions for relative power and at F4 for absolute power. The ratio of high:low frequencies was reduced at P3, P4, T5, T6, O1 and O2 following bupivacaine. Levobupivacaine, on the other hand, produced much fewer EEG changes than bupivacaine. Levobupivacaine decreased relative power in the high alpha band and the ratio of high:low frequencies at T6 only. Absolute power in the theta band was increased at P4, and absolute power in the high alpha band was decreased at F4 and P3, following levobupivacaine. There was an interaction between treatment and time in the absolute high beta band such that high beta increased across the bupivacaine sessions but not in the other conditions.

Levobupivacaine produced fewer changes in the EEG when compared with bupivacaine, both in terms of the number of electrodes in which changes occurred and the magnitude of the effect. Levobupivacaine decreased high alpha power in the parietal, temporal and occipital regions, but to a lesser extent than bupivacaine. Levobupivacaine had no effect on high alpha power in the frontal and central regions, nor did it produce the increase in theta power, observed at some electrodes following bupivacaine.

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REVIEWER'S EFFICACY DISCUSSION

Dr. Bob Rappaport, Deputy Division Director and neurologist was called upon to analyze this study report, in light of the primary reviewer's expertise being in the area of anesthesiology. Upon review of the data presented, Dr. Rappaport was in agreement with the sponsor's conclusion, i.e., levobupivacaine produced fewer changes in the EEG when compared with bupivacaine; however, his overall impression was that the clinical usefulness of this finding was insignificant.

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EFFICACY FINDINGS

OVERVIEW OF CLINICAL STUDIES

Twenty-two adequate and well-controlled clinical trials have been submitted to this NDA in support of the sponsor's claim for use in obstetrics, central and peripheral blocks, pain management and in pediatric populations. A total of 1370 patients have been enrolled from 31 study sites. Only data from 1348 patients was available for data integration and therefore is included in the integrated database.

The efficacy studies were all randomized, active-controlled (bupivacaine), parallel group and double blind in design. Across the adult studies, patients were over 18 years of age, ASA I to II and were scheduled for surgery for which the use of a local anesthetic technique was appropriate. Efficacy endpoints were time to onset of block, duration of block, quality of block, need for rescue medication, and pain scores.

Additionally, the efficacy studies included comparisons between levobupivacaine and lidocaine as well as an evaluation of the efficacy of levobupivacaine when co-administered with narcotic analgesics. The product has been studied as an infusion as well as in bolus administration.

SUMMARY OF STUDIES PERTINENT TO EFFICACY:

STUDY # 030632

PROTOCOL SYNOPSIS:

Title: "A Double-Blind Randomized Controlled Trial of 0.5% Levobupivacaine Compared to 0.5% Bupivacaine for Extradural Anaesthesia in Patients Undergoing Elective Caesarean Section"

Primary Objective: "To compare the efficacy and safety of 0.5% levobupivacaine with that of 0.5% bupivacaine for extradural anaesthesia in patients undergoing Caesarean section."

Secondary Objective: "To determine maternal and neonatal blood levels following use of 0.5% levobupivacaine and 0.5% bupivacaine at the time of delivery."

[Item 8, Vol. 1.53, p. 025]

Study Design:

The study is designed as a randomized, double-blind, parallel group comparative study of 0.5% levobupivacaine versus 0.5% bupivacaine in obstetric patients scheduled for elective cesarean section under epidural anesthesia. The protocol calls for two groups of thirty patients to each be randomly assigned to one of two treatment arms. Approximately 30 patients are to be randomized at each of two sites in Scotland.

Eligible patients will undergo a brief screening phase followed by a 1:1 randomization (30 patients per group) to receive either 0.5% levobupivacaine or 0.5% bupivacaine via epidural catheter, just prior to an elective cesarean section. A total of 25 ml of study medication is administered over 15 min. If at 30 minutes, patients are inadequately blocked for surgery to proceed, an additional 5 ml of study drug is administered over 5 minutes. By protocol amendment, an additional 10 ml of study drug is permitted, if the planned surgery is of such duration to warrant additional dosing. If there is no or inadequate block achieved after the maximal allowable dose is administered, the patient will be withdrawn from the study.

Group I	0.5% levobupivacaine
Group II	0.5% bupivacaine

Eligible patients will be ASA Class I or II females between 18 and 40 years of age, at full-term pregnancy, i.e., more than 37 weeks, carrying no more than two healthy babies. Patients must have no prior history of diabetes, emergency cesarean section or currently be under treatment for pre-eclampsia.

The "pin-prick" method of sensory block will be used to determine the level of block at 0, 2, 5, 10, 15, 20, 25, 30, 45 and 60 min or until a block of T4 -T6 is achieved. Thereafter, the "pin-prick" method of sensory block will be used every 30 minutes until the block has regressed to T10. Subsequently sensory blockade will be assessed hourly until full recovery is achieved. The primary measure of efficacy will be the time to onset of adequate block, i.e., adequate for surgery.

Additionally, during surgery the patients will record their pain level using the Visual Analog Scale (VAS). The investigator will use the modified Bromage scale to assess level of motor blockade at 5, 15, 30 and 60 min, followed by assessments every 30 min until full return of motor function. The anesthetist and obstetrician will measure the level of muscle relaxation using a scale from 0 to 4, where 0 = worst and 4 = best and then give an overall assessment of the quality of the block using a categorical scale where 0 = failure and 2 = satisfactory block.

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STATISTICAL ANALYSIS

"The primary measure of efficacy was time to onset of block adequate for surgery defined as the time from completion of the extradural injection until the time at which both sides of the T5 dermatome did not respond to sensory touch or one side is at T4 and the other side is at T6." [Item 8, Vol. 53, p. 042]

The protocol calls for the following statistical analysis of the primary efficacy endpoints:

"The confirmatory efficacy analysis was to focus on the question of whether the mean difference in time to onset of block adequate for surgery between the 2 study drugs was within the pre-defined 'equivalence criteria', i.e. within ± 10 min." [Item 8, Vol. 53, p. 041A]

The proportion of patients in each group with 'protocol failed blocks' were to be compared between treatment groups using logistic regression with terms for treatment and centre. The significance level of the treatment effect was to be investigated using the Wald statistic. The odds ratio of the treatment difference and the associated 95% confidence interval were to be calculated."

"For those patients who achieved a 'protocol adequate block', time to onset of protocol adequate block was to be analysed using analysis of variance (ANOVA) with terms for treatment, centre and treatment by centre interaction. If the interaction term was not significant at the 10% level it was to be dropped from the model (i.e., main and interaction effects were to be declared significant at the 5% and 10% levels respectively). Using the error variance from the ANOVA, comparison of the treatment LS Means (ie means adjusted for any imbalance in the design) were to be made using a Student's 't'-test. Estimates of treatment difference and associated 90% confidence interval were to be calculated. If the 90% confidence interval should lie within the acceptance range of -10 to 10 min then the 2 study drugs were to be judged equivalent."

"The residuals from this analysis were to be submitted to a Shapiro-Wilk test for normality and examined graphically to assess variance homogeneity. Any deviation from either assumption was to entail a re-analysis using an appropriate alternative transformation of the data e.g. log transformation. Furthermore, following examination of these data, non-parametric methods were to be used if the above methods were not considered appropriate."

"Time to onset of protocol adequate block was to be summarised by treatment group and illustrated graphically using a Kaplan-Meier curve. All patients who did not achieve a 'protocol adequate block' were to be included in the graph as censored observations."

[Item 8, Vol. 1.53, p 043-044]

Secondary Efficacy Variables are:

- 1) "Time to onset of 'clinically adequate block' i.e., time from the completion of the extradural injection until the time when the investigator considered the block adequate for surgery (not necessarily T5 bilaterally)."
- 2) "Time to onset of sensory block i.e. time from completion of extradural injection until first time absence of pain to pinprick is recorded in any dermatome."
- 3) "Time to sensory block offset, i.e. the time from completion of extradural injection until time to complete return of sensory touch in all dermatomes. No attempt was to be made to replace missing values."
- 4) "Proportion of patients recording any motor block prior to surgery."
- 5) "Proportion of patients responding at each grade of motor block."
- 6) "Time to offset of motor block, i.e., time from completion of extradural injection until time where full movement has returned to both sides. No attempt was to be made to replace missing values"
- 7) "Average quality of analgesia, i.e., mean of non-missing pain scores recorded at time of incision, time of abdominal opening, time of uterine incision and in the recovery room. If all 4 scores were missing, no attempt was to be made to replace them."
- 8) "Muscle relaxation assessed by anaesthetist and obstetrician using a 5 point rating scale (0 = worst, 4 = best)."
- 9) "Overall assessment of block by anaesthetist and obstetrician using a 3-point rating scale (0 = failure, 1 = unsatisfactory block, 2 = satisfactory block)."
- 10) "Proportion of patients requiring extra 10 ml of study drug during surgery."

"With the exception of 4, 5, 8, 9 and 10 above, all other secondary endpoints were to be analysed using ANOVA methods as described above for the 'per-protocol' population only. The 2 treatments were to be judged equivalent if the 90% confidence interval for the difference lies within $\pm 10\%$ of the bupivacaine group mean."

"The proportion of patients recording any motor block prior to surgery, the distribution of patients recording each grade of motor block, muscle relaxation and overall assessment (for anaesthetist and obstetrician separately) and the proportion of patients requiring extra 10 ml of study drug during surgery were to be analysed using a logit model with terms for centre and treatment for the 'per-protocol' population only. The significance level of the treatment effect was to be investigated using the Wald statistic. The odds ratio of the treatment difference and the associated 95% confidence interval was to be calculated. The logit model assumes proportional odds across the categories of the response variable. The validity of this assumption was to be tested using the score test statistic for goodness-of-fit. If this assumption was clearly not satisfied, non-parametric methods were to be used.

"Time to onset and offset of sensory block, time to offset of motor block and average quality of analgesia were to be summarised by treatment using descriptive statistics."

"The proportion of patients recording motor block prior to surgery and the proportion of patients achieving each grade of motor block and the proportion of patients requiring extra 10 ml of study drug during surgery were to be presented by treatment group. The distribution of patients in each category of muscle relaxation and overall assessment of block were to be presented by treatment."

"Sensory block were to be tabulated by treatment and illustrated graphically. Scores were to be assigned to each dermatome as follows: score of 1 to dermatome C1, 2 to dermatome C2, ..., 29 to dermatome S4 and 30 to dermatome S5. The spread of the sensory block at each assessment was then to be tabulated and illustrated graphically using the treatment group medians and their respective interquartile range. The medians, interquartile range and y-axis were to be reformatted to the dermatome name instead of the scores."

PROTOCOL AMENDMENT:

This amendment was dated 1/27/97. It consists of three changes in the clinical section of the protocol as follows:

A. Drug Administration

- Addition of the following statement: "Where required, if the duration of surgery necessitates additional block, then a further 10 ml of study drug may be administered"

B. Screening/Entry/Randomization

- 12 lead ECG will be eliminated from the screening procedures.

C. Extradural Anaesthesia

- The dose of ephedrine used to treat hypotension will be decreased from 5 mg to 3 mg.

The amendment calls for changes to the pharmacokinetics section as follows:

A. Pharmacokinetic Samples- A final paragraph will be added as follows:

"The measured drug concentration vital signs time curve will be produced. The profiles will be presented in tabular and graphical form for each subject. Summary statistics will be calculated for plasma concentrations for each time point and study drug. Using a model independent approach, the following values will be calculated for each subject:

- Area under the plasma drug concentration vital signs time curve (AUC)
- Peak plasma drug concentration (C_{max})
- Time of peak plasma concentration (T_{max})
- Terminal half life ($T_{1/2}$)"

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CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 69 patients randomized, 67 (97.1%) received study medication and were considered to be evaluable for the safety analyses. Of the 69 patients randomized, 2 patients were withdrawn prior to study drug administration. Patient 007 experienced a technical failure during the conduct of his epidural, i.e., dural puncture, prior to study drug administration and; consent was withdrawn by patient 018's consultant, [Note: the sponsor uses the term consultant which likely refers to the patient's obstetrician/primary care physician] also before drug administration.

Of the 67 patients who received the study drug, 3 patients were withdrawn secondary to protocol violations and additional 2 patients received prohibited medication prior to dosing. Therefore, only 62 patients (31 levobupivacaine and 31 bupivacaine) were considered 'per protocol'. Of those patients eligible for the 'per-protocol' population, a total of 5 patients (2 levobupivacaine, 3 bupivacaine) did not achieve a 'protocol adequate block' (i.e., did not achieve a bilateral T5 block prior to surgery) and therefore only 57 patients (82%) were eligible for analysis of the primary measure of efficacy.

Specifically, the 2 patients (047 and 054) who received prohibited pre-dose medication (dihydrocodeine and cocodamol, respectively) were in the bupivacaine group and from Center 001. Patient 049 from Center 001 received levobupivacaine and was said to have had a failed block (reason not provided) and patients 057 and 066 who were only said to have experienced, "technical failures" (type not provided) received levobupivacaine and bupivacaine respectively and were both from Center 002.

The protocol calls for a second epidural injection of study drug, if needed, to achieve an adequate block or to maintain an adequate block (bilateral T5). Four patients in the levobupivacaine group versus two patients in the bupivacaine group received a second epidural injection of study drug (5 ml) despite already having achieved an adequate block (bilateral T5). Additionally, seven patients in the levobupivacaine group versus 5 patients in the bupivacaine group did not receive a second dose (5 ml) despite not achieving an adequate level of block at 15 minutes as is required in the protocol. Of interest is the potential impact this protocol violation may have on such endpoints as duration of block and quality of anesthesia, as well as, it's effect on safety findings. The statistical ramifications of this violation will be discussed by the reviewing statistician.

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Table 2. Patient Disposition

PATIENT NUMBER	0.5% LEVOBUPIVACAINE N (%)	0.5% BUPIVACAINE N (%)	PATIENT TOTALS N (%)
Randomized	35	34	69 (100)
Excluded from Safety Population	2	0	2
Safety Evaluable	33 (94.2)	34 (100)	67 (97.1)
Excluded from Intent-to-Treat:	2	1	3
Intent-to-Treat Population	31 (88.6)	33 (97)	64 (92.7)
Excluded from Per-Protocol:	0	2	2
Per-protocol Population	31 (88.6)	31 (91.2)	62 (89.8)
Excluded from Evaluable Primary Efficacy Patients:	2	3	5
Evaluable Primary Efficacy Patients:	29 (83)	28 (82.3)	57 (82.6)
5 (0.07%) Total Discontinued from Study			64 (92.7%) Total Completed

[based on sponsor's Table 3.1, Item 8, Vol. 1. 53, p. 086]

Protocol violations are summarized for individual patients in the table below.

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Table 3. PATIENT SPECIFIC PROTOCOL VIOLATIONS

PROTOCOL VIOLATION	TREATMENT	PATIENT NUMBERS
Entry Criteria:		
Patient's consultant withdrew consent	0.5% Levobupivacaine	018
Received Prohibited Pre-Dose Medication	0.5% Bupivacaine	047,054
Technical Failure	0.5% Levobupivacaine	007 ,057
	0.5% Bupivacaine	066
Did Not Achieve Bilateral T5 Block	0.5% Bupivacaine	009,017, 019
	0.5% Levobupivacaine	001, 010
Failed Block	0.5% Levobupivacaine	049

Patients did not receive study medication.

[taken from sponsor's Table 3:3 and Table 2.1,Item 8, Vol. 1.53, p. 088 and 84, respectively]

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Demographics

The following table summarizes the demographic characteristics of the two treatment groups:

Table 4. Demographics - Safety Evaluable Population

	STATISTICS	0.5% LEVOBUPIVACA INE	0.5% BUPIVACAINE
Age (years)	n	33	34
	mean	28.7	30.4
	s.d.	5.9	4.8
	range	18-39	22-40
Women	%	100	100
Race:			
Caucasian	n	32	33
Hispanic	n	1	0
Asian	n	0	1
Weight (kg)	n	33	34
	mean	75.63	78.05
	s.d.	11.56	12.60
Height (cm)	n	33	34
	mean	161.5	160.7
	s.d.	5.4	6.6

[based on sponsor's Table 4.1, Item 8, Vol.1.53, p. 089]

Patients' ages ranged from 18-40 years and were at term pregnancy with a mean gestational age of 38.26 weeks and 38.03 weeks for the Levobupivacaine and Bupivacaine groups, respectively. 74.2 % of evaluable patients in the levobupivacaine treated group were multipara compared with 71.0% of the bupivacaine treated group. 38.7% (12 patients) and 51.6% (16 patients) in the levobupivacaine and bupivacaine 'per protocol' population had a history of Cesarean section.

The overall medical histories at screening, as described below, demonstrated 0% of patients in the levobupivacaine group and 1% of patients in the bupivacaine group to have no medical history/concomitant diseases. The most commonly reported medical condition was anemia of pregnancy, which was present in 46.4% of patients. Heartburn was present in 34.8%, edema in 24.6%, asthma in 13%, and allergy to antibiotics in 7.2% of patients.

Table 5. Medical History at Screening - All Patients

Body System/Procedures	Treatment			
	0.5% Levobupivacaine		0.5% Bupivacaine	
	N	%	N	%
Infectious and parasitic	3	9.1	4	11.8
Neoplasms	1	3.0	1	2.9
Endocrine, nutritional	2	6.1	1	2.9
Blood and blood-forming	0	0	3	8.8
Mental disorders	1	3.0	3	8.8
Nervous System and Sense	3	9.1	4	11.8
Circulatory system	2	6.1	1	2.9
Respiratory system	9	27.3	11	32.4
Digestive system	12	36.4	7	20.6
Genitourinary system	6	18.2	7	20.6
Pregnancy, child birth and	22	66.7	24	70.6
Skin and subcutaneous tissue	4	12.1	5	14.7
Musculoskeletal system and	2	6.1	2	5.9
Congenital anomalies	2	6.1	0	0
Symptoms, signs and ill-	10	30.3	10	29.4
Injury and poisoning	3	9.1	6	17.6
Endoscopy	3	9.1	3	8.8
Other procedures for diagnosis	1	3.0	0	0
Endocrine function tests and	0	0	2	5.9
Ancillary procedures other than	2	6.1	0	0
Injury undetermined-	1	3.0	0	0
No medical	0	0	1	2.9

Note: Multiple diseases in the same body system have been counted once per patient

[taken from sponsor's Table II, Item 8, Vol. 1.53, p. 057]

All patients except patient 050 reported concomitant medications. Baseline medications were primarily stopped on study entry; those that continued into the study or were started during the study were not considered to interfere with the study results. They included such drugs as oxytocin to increase uterine tone, analgesics for post-operative pain and prophylactic antibiotics.

All patients took preoperative antacids for aspiration prophylaxis. 95.5% of patients received medications for the musculoskeletal pain and 82.1% of patients were given such drugs as ephedrine for hypotension and anti-emetics for nausea and vomiting.

Table 7 below is a table listing of concomitant medications taken prior to epidural injection and continuing into the study and Table 8 summarizes the concomitant medications administered post-dose by treatment group.

Table 6. Screening Medications Details

	Treatment			
	Levobupivacaine		Bupivacaine	
	N	%	N	%
Alimentary tract and metabolism	1	3.0	2	5.9
Blood and blood forming organs	5	15.2	7	20.6
Dermatologicals	1	3.0	1	2.9
Systemic hormonal prep. excl. sex hormones	1	3.0	0	0
General anti-infectives for systemic use	0	0	1	2.9
Central nervous system	0	0	1	2.9
Respiratory system	6	18.2	4	11.8
Various	1	3.0	1	2.9
None	22	66.7	23	67.6

Note: Multiple medications in the same therapeutic class have been counted once per patient

Table 7. Concomitant Medications Details

	Treatment			
	Levobupivacaine		Bupivacaine	
	N	%	N	%
Alimentary tract and metabolism	8	24.2	15	44.1
Blood and blood forming organs	17	51.5	17	50.0
Genito-urinary system and sex hormones	3	9.1	1	2.9
Systemic horm.l prep., excl. sex horm.	33	100	34	100
General anti-infectives for systemic use	33	100	34	100
Musculo-skeletal system	31	93.9	33	97.1
Central nervous system	33	100	34	100
Respiratory system	25	75.8	30	88.2
Sensory organs	2	8.1	0	0
Various	7	21.2	7	20.8
Uncoded	1	3.0	2	5.9

Note: Multiple medications in the same therapeutic class have been counted once per patient

[taken from sponsor's Table III and IV, Item 8, Vol. 1.53, p. 059]

SPONSOR'S EFFICACY RESULTS:

Treatment-by-site Interaction:

The proportion of 'per-protocol' patients not achieving 'per-protocol adequate block' were all recruited in Center 2. There was evidence of difference between centers, with the mean time to onset of block being longer in Center 2. A total of 6.5% (2/31) of levobupivacaine patients did not achieve 'protocol adequate block' compared with 9.7% (3/31) bupivacaine patients. The Wald statistic for a treatment difference was not statistically significant ($p=0.64$).

Primary Efficacy Variables:

The primary efficacy variable is time to onset of 'protocol adequate block' (bilateral T5 block). The mean time to onset of 'protocol adequate block' was 10.2 and 9.0 min for levobupivacaine and bupivacaine, respectively. The treatment difference was estimated as 1.6 min. As the 90% confidence interval lies within ± 10 min, the 2 treatments can be judged equivalent with respect to time to onset of 'protocol adequate block'.

Table 8. Time to Onset of Protocol Adequate Block (minutes) – Per-protocol Population

	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
Mean	10.2	9
Median	10	10
SD	7.2	6.7
Min	0	0
Max	30	25
N	29	28

[taken from sponsor's Table 8.3.2 Item 8, Vol. 1.53, p. 110]

Secondary Efficacy Variables:

Time to Onset of Clinically Adequate Block

The mean time to onset of 'clinically adequate block' (adequate for surgery to proceed) was 12.6 and 11.4 min for levobupivacaine and bupivacaine respectively. The treatment difference was estimated as 1.5 min. The treatment difference was estimated as 1.6 min. As the 90% confidence interval lies within ± 10 min, the 2 treatments can be judged equivalent with respect to time to onset of 'clinically adequate block'.

Table 9. Time to Onset of Clinically Adequate Block (minutes) Per-protocol Population

	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
Mean	12.6	11.4
Median	6.8	6
SD	13	10
Min	2	0
Max	30	25
N	31	31

[taken from sponsor's Table 9.2, Item 8, Vol. 1.53, p. 112]

Time to Onset of Sensory Block

Eighty-seven percent of patients (27/31) in both treatment groups recorded onset times of zero which is said to mean that some level of sensory block had occurred immediately after completion of the epidural. The distribution of onset times were said to be well balanced between treatment groups and the Cochran-Mantel-Haenzel Test was not significant ($p=0.65$).

Table 10. Time to Onset of Sensory Block – Per-protocol Population

MINUTES	0.5% LEVOBUPIVACAINE						0.5% BUPIVACAINE					
	001		002		ALL		001		002		ALL	
	N	%	N	%	N	%	N	%	N	%	N	%
0:00	1	10	1	76	2	87	1	83	1	89	2	8
	4	0	3		7		0		7		7	7
0:01	0	0	0	0	0	0	1	8	0	0	1	3
0:02	0	0	3	18	3	10	1	8	2	11	3	1
											0	0
0:03	0	0	2	6	1	3	0	0	0	0	0	0
ALL PATIENTS	1	10	1	10	3	10	1	10	1	10	3	1
	4	0	7	0	1	0	2	0	9	0	1	0
											0	0

[taken from sponsor's Table 10, Item 8, Vol. 1.53, p. 113]

Time to Offset of Sensory Block

The mean time to offset of sensory block was 485.9 minutes (range 282 to 793 min) and 462.7 minutes (range 225 to 835 min) for levobupivacaine and bupivacaine respectively. The treatment difference was estimated as 19 min (90% CI: -37, 75). As the 90% confidence interval does not lie within $\pm 10\%$ of the bupivacaine mean, the two treatments cannot be judged equivalent with respect to the time of offset of sensory block. Additionally, the sponsor reports that as the 90 % confidence interval contains zero, it cannot be ruled out that there is no difference between the 2 treatment groups.

The sponsor reports that there was evidence of difference between centers (mean time to offset of sensory block being longer in Center 001) with respect to this variable.

Table 11. Time to Offset of Sensory Block - Per Protocol Population

	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
Mean	485.9	462.7
Median	435	430
SD	142.8	137.4
Min	282	225
Max	793	835
N	29	29

[taken from sponsor's Table 11.2, Item 8, Vol. 1.53, p. 115]

Proportion of Patients Recording Motor Block Prior to Surgery

Forty-two percent (13/31) of levobupivacaine patients had no motor block prior to surgery compared with 26% (8/31) of bupivacaine patients. The odds ratio (levobupivacaine/bupivacaine) was 2.03 (95% CI: 0.66, 6.23). The sponsor reports that the odds of having no motor block prior to surgery are estimated to be 2.03 times higher in the levobupivacaine group compared with bupivacaine with the Wald statistic showing no statistically significant treatment difference (P=0.22).

Table 12. Proportion of Patients Recording Any Motor Block Prior to Surgery-Per - Protocol Population

	0.5% LEVOBUPIVACAINE		0.5% BUPIVACAINE	
	N	%	N	%
YES	18	58	23	74
NO	13	42	8	26
ALL PATIENTS	31	100	31	100

Time to Offset of Motor Block

The sponsor has found evidence of a difference between centers i.e., the mean time to offset of motor block was found to be longer in Center 001. Additional findings are as follows: "The mean (median) time to offset of motor block was 241.9 (206.5) [range 75 to 555] and 171.8 (163.5) [range 85 to 340] min for levobupivacaine and bupivacaine, respectively. The treatment difference was estimated as 48.0 min (90% CI: 10.0, 90.0). This means that on average, the time to offset of motor block is expected to be 48 min longer following levobupivacaine compared with bupivacaine. As the confidence interval does not lie within $\pm 10\%$ of the bupivacaine mean, the 2 treatments cannot be judged equivalent with respect to the time to offset of motor block."

Clinically, such a lengthy difference in the time to offset of motor block is relevant.

Nine levobupivacaine patients and 3 bupivacaine patients did not record any motor block and have been excluded from the summary tables and statistical analysis.

Maximum Grade of Motor Block Reported During Study

The sponsor has found that, "ten percent (3/31) of levobupivacaine patients recorded a maximum motor block of Grade 3 compared with 16% (5/31) of bupivacaine patients. Maximum motor block of at least Grade 2 was recorded by 23% (7/31) of levobupivacaine patients compared with 42% (13/31) bupivacaine patients. Seventy one percent (22/31) of levobupivacaine patients recorded some motor block compared with 90% (28/31) of bupivacaine patients. This means that the odds of having increased motor block are estimated to be 0.36 times higher in the levobupivacaine group compared with bupivacaine (ie odds of having increased motor block are estimated to be 2.78 times higher in the bupivacaine group compared with levobupivacaine). The Wald statistic for a treatment difference was statistically significant (P=0.037)."

[taken from Item 8, Vol. 1.53, p. 066-067]

Average Quality of Analgesia

The average quality of anesthesia was determined using the Visual Analogue Pain Score (VAS), which was measured at skin incision, abdominal opening, uterine incision and in the recovery room using a 100 mm scale. It was defined as the mean of the 4 measures. The sponsor reports the following findings: "The mean (median) average quality of analgesia was 8.28 (2.33) [range 0.0 to 52.5] and 4.46 (0.25) [range 0.0 to 20.0] mm for levobupivacaine and bupivacaine respectively. The treatment difference was estimated as 0.0 mm (90% CI: 0.0, 2.5). This means that on average, the average quality of analgesia is expected to be the same following levobupivacaine and bupivacaine. As the 90% confidence interval contains zero, it cannot be ruled out that there is no difference between the two treatment groups. However, as the confidence interval does not lie within $\pm 10\%$ of the bupivacaine mean (equivalence criteria defined in the protocol), the 2 treatments cannot be judged equivalent with respect to the average quality of analgesia."

[taken from Item 8, Vol. 1.53, p. 066-067]

Muscle Relaxation (Proportion of Patients Responding at Each Grade of Motor Block)

Muscle relaxation was assessed by both the anesthesiologist and the obstetrician using a 5 point rating scale, where 0=worst and 4=best. The sponsor reports that, "six percent (2/31) of levobupivacaine patients were assessed by the anaesthetist as 'best' compared with 19% (6/31) of bupivacaine patients. Ninety four percent (29/31) of levobupivacaine patients were assessed by the anaesthetist as 'good' or 'best' compared with 90% (28/31) of bupivacaine patients. All patients were assessed as at least 'fair'. The odds ratio (levobupivacaine/bupivacaine) was 0.62 (95% CI: 0.18, 2.17). This means that the odds of having better muscle relaxation are estimated to be 0.62 times higher in the levobupivacaine group compared with bupivacaine (*i.e.* odds of having better muscle relaxation are estimated to be 1.61 times higher in the bupivacaine group compared with levobupivacaine). The Wald statistic for a treatment difference was not statistically significant ($p=0.46$).

Six percent (2/31) of levobupivacaine patients were assessed by the obstetrician as 'best' compared with 13% (4/31) of bupivacaine patients. Ninety four percent (29/31) of levobupivacaine patients were assessed by the obstetrician as 'good' or 'best' compared with 87% (27/31) of bupivacaine patients. Ninety seven percent (30/31) of levobupivacaine patients were assessed by the obstetrician as at least 'fair' compared with 100% (31/31) of bupivacaine patients. The odds ratio (levobupivacaine/bupivacaine) was 1.04 (95% CI: 0.30, 3.63). This means that the odds of having better muscle relaxation are estimated to be 1.04 times higher in the levobupivacaine group compared with bupivacaine. The Wald statistic for a treatment difference was not statistically significant ($p=0.96$)."

[taken from Item 8, Vol. 1.53, p. 067-068]

Overall Assessment of Block

The overall assessment of block was performed by both the anesthesiologist and the obstetrician using a 3 point rating scale where 0 = failure, 1 = unsatisfactory block, and 2 = satisfactory block. According to the sponsor, "Fifty - five percent (17/31) of levobupivacaine patients were assessed as 'satisfactory' by the anaesthetist compared with 77% (24/31) of bupivacaine patients. The odds ratio (levobupivacaine/bupivacaine) was 0.36 (95% CI: 0.12, 1.08). This means that the odds of having 'satisfactory' block are estimated to be 0.36 times higher in the levobupivacaine group compared with bupivacaine (*i.e.*, the odds of having 'satisfactory' block are estimated to be 2.78 times higher in the bupivacaine group compared with levobupivacaine). The Wald statistic for a treatment difference was not statistically significant ($p=0.069$). Eighty - seven percent (27/31) of levobupivacaine patients were assessed as 'satisfactory' by the obstetrician compared with 90% (28/31) of bupivacaine patients. The odds ratio (levobupivacaine/bupivacaine) was 0.72 (95% CI: 0.15, 3.55). This means that the odds of having 'satisfactory' block are estimated to be 0.72 times higher in the levobupivacaine group compared with bupivacaine (*i.e.* the odds of having 'satisfactory' block are estimated to be 1.39 times higher in the bupivacaine group compared with levobupivacaine). The Wald statistic for a treatment difference was not statistically significant ($P=0.69$)."

[taken from Item 8, Vol. 1.53, p. 068-69]

Proportion of Patients Receiving Extra 5 ml of Study Drug

The protocol allows for an injection of an optional 5 ml of study drug, if needed, following the administration of the required 22ml bolus dose. Additionally, the amended protocol allows for an additional injection of 10ml of study drug, if the duration of surgery necessitates an additional dose. The proportion of patients requiring the 10ml of study drug during surgery was to be considered a secondary endpoint. However, the endpoint that was analyzed is the proportion of patients receiving an extra 5 ml of study drug during the conductance of the epidural. The sponsor gives no explanation for this change in secondary endpoints.

The analysis performed is as follows: "A total of 10% (3/31) of levobupivacaine patients received the additional injection, [*i.e.*, 5 ml of study drug] compared with 3% (1/31) of bupivacaine patients. The Wald statistic for a treatment difference was not statistically significant ($P=0.32$).

APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S EFFICACY DISCUSSION

The primary efficacy variable - time to onset of protocol adequate block - for 0.5% levobupivacaine and 0.5 % bupivacaine was judged equivalent. As the 90 % confidence interval lies within ± 10 min (i.e., 1.6 min) the 2 treatments were judged equivalent with respect to time to onset of 'protocol adequate block'.

The analysis of the secondary endpoints revealed the following results:

1. Time to offset of sensory and motor block which were judged not to be equivalent; however, because the confidence interval contains zero, it cannot be ruled out that there is no difference between them either.
2. Average quality of analgesia which showed that neither can it be ruled out that there is no difference between the two drugs, nor can they be ruled equivalent, and
3. Muscle relaxation which showed that, according to the anesthesiologists, bupivacaine-treated patients had better muscle relaxation; however, according to the obstetricians, levobupivacaine-treated patients had better muscle relaxation, and
4. Overall assessment of block which showed that according to the both anesthesiologists and obstetricians, bupivacaine-treated patients had better overall block, and
5. Proportion of patients recording motor block prior to surgery - no statistically significant difference was found between the two treatments; however, the odds of having no motor block prior to surgery are 2.03 times higher in the levobupivacaine group, and
6. Time to onset of sensory block - no statistically significant difference was found between the two treatments, and
7. Proportion of patients receiving extra 5 ml of study drug - no statistically significant difference was found between the two treatments.

The reported lengthy difference in the time to offset of motor block between levobupivacaine and bupivacaine (i.e., levobupivacaine demonstrated a longer time to offset of motor block) is clinically relevant. Today's practice of anesthesiology is focused on quick patient turn-around. In other words, ideally, all surgical patients will be treated and released in the same day and within the shortest possible time. If drug has been shown to cause a substantially longer length of motor block over bupivacaine (one of the more commonly used long-acting muscle relaxants) it is likely to be of little usefulness in today's clinical practice.

Overall, the clinical data proves that the product, 0.5% levobupivacaine, is effective when administered as an epidural infusion to obstetric patients undergoing a cesarean section. This conclusion is based upon the clear evidence that patients experienced some level of analgesia sufficient for cesarean section.

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STUDY # CS-001**PROTOCOL SYNOPSIS:**

Title: "A Double Blind Randomized Controlled Trial of 0.5% Levobupivacaine Compared to 0.5% Bupivacaine for Epidural Anaesthesia in Patients Undergoing Elective Caesarean Section"

Primary Objective: "To demonstrate that 0.5% levobupivacaine and 0.5% bupivacaine are equally efficacious."

Secondary Objective: "To determine time to offset of sensory block, time to onset and offset of motor block, time to onset of anesthesia, quality of anesthesia, muscle relaxation, and overall assessment."

[item 8, Vol. 1. 55, p. 004]

**APPEARS THIS WAY
ON ORIGINAL**

Study Design:

The study is designed as a randomized, single center, double blind, parallel group, and comparative study of 0.5% levobupivacaine versus 0.5% bupivacaine in obstetric patients scheduled for elective cesarean section under epidural anesthesia. The protocol calls for two groups of thirty patients to each be randomly assigned to one of two treatment arms.

Eligible patients will undergo a brief screening phase followed by a 1:1 randomization (30 patients per group) to receive either 0.5% levobupivacaine or 0.5% bupivacaine via epidural catheter, just prior to an elective cesarean section. The night before surgery, patients will fast starting at 12:00 midnight. On the morning of surgery, they will undergo a physical examination, followed by receiving Bicitra (sodium citrate and citric acid) 30 mg orally and metoclopramide 10 mg iv. over 30 min.

Group I	0.5% levobupivacaine
Group II	0.5% bupivacaine

Eligible patients will be ASA Class I or II females between 18 and 40 years of age, at full-term pregnancy, i.e., more than 37 weeks gestational age, carrying no more than two healthy babies. Patients must have no prior history of diabetes, emergency cesarean section or currently be under treatment for pre-eclampsia.

The "pin-prick" method of sensory block will be used to determine the level of block at 0, 5, 10, 15, 20, 25, 30, 45 and 60 min or until a block of T4 -T6 is achieved. Thereafter, the "pin-prick" method of sensory block will be used every 30 minutes until the block has regressed to T10. Subsequently, sensory blockade will be assessed hourly until full recovery is achieved. The primary measure of efficacy will be the time to onset of adequate block, i.e., adequate to carry out cesarean section.

Additionally, during surgery the patients will record their pain level using the Visual Analog Scale (VAS), where 0 = no pain and 100 = very painful. These measurements will occur at the time of skin incision, abdominal opening, uterine incision and manipulation and in the recovery room.

The investigator will use the modified Bromage scale (0 = no paralysis and 3 = inability move lower limb) to assess level of motor blockade at 5, 15, 30 and 60 min, followed by assessments every 30 min until full return of motor function. The anesthetist and obstetrician will measure the level of muscle relaxation using a scale from 0 to 4, where 0 = worst and 4 = best and then give an overall assessment of the quality of the block using a categorical scale where 0 = failure and 2 = satisfactory block.

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- K. Discontinuation
- Deleted the requirement for a patient final evaluation following discontinuation.
- L. Pharmacokinetic Analysis Procedure
- Added "Time 0" to the procedure for obtaining blood samples.
- M. Primary Objective
- The primary objective has been revised to read as follows: *"The primary objective of this trial is to demonstrate that 0.5% levobupivacaine and 0.5% bupivacaine are equally efficacious. The primary efficacy endpoint is time to onset of sensory block adequate to carry out surgery."*
 - The previous wording was as follows: "To compare the efficacy of levobupivacaine with bupivacaine when used for epidural anesthesia. The primary efficacy endpoints include onset of anesthesia, offset of anesthesia, and quality of anesthesia."
- N. Secondary Objective
- The secondary objective has been revised to read as follows: *"The secondary objectives are to determine time to offset of sensory block, time to onset and offset of motor block, time to onset of anesthesia, quality of anesthesia, muscle relaxation, and overall assessment. The safety objectives are to determine maternal and neonatal blood levels following use of 0.5% levobupivacaine and 0.5% bupivacaine at the time of delivery."*
 - The previous wording was as follows: "To determine maternal and neonatal blood levels following use of 0.5% levobupivacaine and 0.5% bupivacaine at the time of delivery."
- O. Safety Analysis Procedures
- Revised the safety analysis procedure to reflect the change as seen below:
- From:
- "Vital signs and ECG data will be summarized in tabular form. QT measurements will be obtained using a 12-lead ECG at pre-dose and at the predicted Tmax. Three beat strips will be obtained from which the Qtc intervals will be calculated.
- The QT interval will examine the change relative to baseline. The QT change will be analyzed by a t-test. If appropriate, a transformation (e.g., logarithmic transformation of the ratio relative to baseline) or non-parametric statistic will be used. A categorical transformation (e.g., >50% increase in interval length) may be used and analyzed by a Fisher Exact test."
- To:
- "Vital signs and normal/abnormal ECG data will be summarized in tabular form and any trends noted.
- 12-lead EKGs collected at pre-dose and at the time of adequate block for surgery will be used to determine QT interval and QT dispersion. QRS duration will be determined from high-resolution scans. Where additional EKGs have been collected from patients undergoing pharmacokinetic sampling, these parameters will be related to drug concentrations if possible. Measurement and analysis of all ECO parameters will be the subject of a separate protocol."

Additionally, the amendments call for administrative changes in the areas of drug storage and accountability, contact persons, references and appendices.

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 65 patients randomized, 63 (96.9%) received study medication and were considered to be evaluable for the safety analyses. Two of the 65 patients randomized, one from each treatment group, were withdrawn prior to study drug administration. Patient 103, randomized to the levobupivacaine treatment group, violated the age criteria - she was 41 years old. Patient 106, randomized to the bupivacaine group, went into labor earlier than expected and had an unscheduled cesarean section.

Of the 63 patients who received the study drug, 1 patient (Patient 171) in the bupivacaine group experienced an intravascular injection and was discontinued from the study. She did not have a post-baseline efficacy evaluation and therefore was not included in the ITT population.

Of the 62 ITT patients, 2 patients (Patients 121 and 169) in the levobupivacaine group were discontinued from the study secondary to treatment failure. They required additional anesthesia beyond the protocol - driven 30 ml of study drug. Therefore, a total of 60 patients were included in the per-protocol population, thirty in each treatment group.

Table 14. Patients Excluded from Efficacy Evaluable Population

PATIENT NUMBER	TREATMENT GROUP
103 ^a	0.5% Levobupivacaine
106 ^b	0.5% Bupivacaine
171 ^c	0.5% Bupivacaine

^a Patient withdrawn prior to receiving study drug - age greater than 40 years
^b Patient withdrawn prior to receiving study drug - unscheduled cesarean section
^c Patient experienced an adverse event (intravascular injection) after receiving study drug, but did not receive post-baseline evaluations

Table 15. Patient Disposition

	LEVOBUPIVACAINE N (%)	BUPIVACAINE N (%)	ALL PATIENTS N (%)
Total Patients Randomized	33 (100)	32 (100)	65 (100)
Withdrawn Prior to Randomized Treatment ¹	1 (3.0)	1 (3.1)	2 (3.1)
Safety Population	32 (97)	31 (96.9)	63 (96.9)
Received Study Drug but No Post-Baseline Efficacy Evaluation ²	0	1 (3.1)	1 (1.5)
ITT Population	32 (97)	30 (93.8)	62 (95.4)
Per Protocol Population	30 (90.9)	30 (93.8)	60 (92.3)
Non-Protocol Evaluable ³	2 (6.1)	0	2 (3.1)
Discontinued	3 (9.1)	2 (6.3)	5 (7.7)
Completed	30 (90.9)	30 (93.8)	60 (92.3)

¹ Patients Nos. 103 and 106 withdrew prior to receiving study drug.

² Patient No. 171 discontinued due to an adverse event.

³ Patients Nos. 121 and 169 discontinued due to inadequate anesthesia.

[taken from sponsor's Table 2, "Patient Disposition: Intent -to-Treat Population", Item 8, Vol. 1.55, p. 048]

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Patient specific protocol violations are summarized for individual patients in the table below. Patients who required additional anesthesia beyond the protocol driven 30 ml are considered to be protocol violators. Two such patients are patients 121 and 169 of the levobupivacaine treatment group. These patients were included in the ITT population for the analysis of efficacy.

Other protocol violations occurred as follows: The investigator assessed sensory block every 30 minutes instead of every hour after T10 block regression, until complete recovery from sensory blockade. At the end of the study the unused study drugs were destroyed when the protocol requires them to be returned to the Sponsor or designee.

Table 16: Patient-Specific Protocol Violations

PROTOCOL VIOLATION	TREATMENT	PATIENT NUMBERS
Entry Criteria:		
Patient's age fell outside of the inclusion criteria	Levobupivacaine	103
Unscheduled Cesarean Section	Bupivacaine	106
Adverse Event	Bupivacaine	171
Failed Block	Levobupivacaine	121, 169

Patients did not receive study medication.

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Demographics

The following table summarizes the demographic characteristics of the two treatment groups:

Table 17. Demographics - Safety Evaluable Population

	STATISTICS	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
Age (years)	n	32	31
	mean	34	33.6
	s.d.	3.02	3.54
	range	28-39	23-40
Women	%	100	100
Race:			
Caucasian	n (%)	26 (81.3)	25 (80.6)
Hispanic	n (%)	0	1 (3.2)
Asian	n (%)	1	4 (12.9)
Weight (kg)	n	32	31
	mean	80.06	81.07
	s.d.	12.873	11.911
Height (cm)	n	32	31
	mean	161.05	162.89
	s.d.	5.029	6.947
Gestation (weeks)	n	32	31
	mean	38.9	38.6
	s.d.	0.76	0.67
	range	38-41	37-40

[based on sponsor's Table 3.1 , Item 8, Vol. 1.58, p. 367-369]

Patients' ages ranged from 23 to 30 with a mean age of 33.7 years. The mean gestation was 38.8 weeks (range 37-41 weeks). The majority of women had given birth more than once (multipara, 75.8%), had undergone at least one previous cesarean section and were Caucasian (80.6%).

The overall medical histories at screening are described in the table below.

Table 18. Medical History

TREATMENT	PATIENT#	BODY SYSTEM	ABNORMALITY
Levobupivacaine	105	Respiratory	Left Leg Sciatic
Levobupivacaine	113	Breast	Fibrocystic Disease
Levobupivacaine	117	Cardiovascular	Asymptomatic Murmur
Levobupivacaine	121	Respiratory	Cough, Cold Last 3 Days
Levobupivacaine	122	Gastrointestinal	Pregnancy-Induced
Levobupivacaine	130	Other	Obesity
Levobupivacaine	133	Respiratory	Asthma - mild
Levobupivacaine	137	Cardiovascular	Mitral Valve Prolapse - mild
Levobupivacaine	142	Ophthalmic	Hypema of Iris and Ciliary
Levobupivacaine	143	Gastrointestinal	Hyperemesis Gravidarum
Levobupivacaine	164	Musculoskeletal	Knee Surgery
Levobupivacaine	166	Gastrointestinal	Ulcerative Colitis
Levobupivacaine	173	Hematopoietic/Lymp	Thallemia Trait
Levobupivacaine	176	Gastrointestinal	Hiatal Hernia - congenital
Levobupivacaine	178	Respiratory	Asthma - no illness since
Levobupivacaine	182	Gastrointestinal	Esophageal Reflux
Bupivacaine	101	Respiratory	Cough X 2 Days
Bupivacaine	102	Respiratory	Asthma - mild
Bupivacaine	107	Respiratory	Cold
Bupivacaine	123	Neurologic	Migraine Headaches - 10
Bupivacaine	124	Musculoskeletal	Back Pain X 1 week
Bupivacaine	136	Other	Chicken Pox During This
Bupivacaine	139	Gynecologic	Left Ovarian Cyst
Bupivacaine	141	Dermatologic	Skin Eruption - lower body
Bupivacaine	168	Musculoskeletal	S/P Left Knee Arthroscopy
Bupivacaine	170	Respiratory Genitourinary	Asthma - inactive H/o Kidney Stones
Bupivacaine	177	Cardiovascular	Heart Murmur, Unknown
Bupivacaine	179	Hematopoietic/Lymp	Anemia
Bupivacaine	181	Cardiovascular	Pregnancy-Induced

[taken from, "Data Listing 3.1", Item 8, Vol. 1.55, p. 079-115]

Of interest are the following medical conditions, which potentially could influence study results. However, the likelihood of them impacting on study results, is remote.

- Sciatica - Patients 105 and 181 - may affect sensory and motor examination
- cardiac murmurs - Patient 117 and 177 - may affect ECG interpretation
- mitral valve prolapse - Patient 137 - may affect ECG interpretation
- joint surgery - Patient 164 and 168 - may affect both sensory and motor examinations
- peroneal nerve damage - Patient 137 - may affect sensory and motor examination
- back pain - Patient 124 and 143 - may affect patients perception of epidural - induced back injury

Table 19. Physical Examinations – Intent-to-Treat Population

Table 4 Physical Examination: Intent-to-Treat Population

Body System	Levobupivacaine (n=32)			Bupivacaine (n=30)		
	Normal N (%)	Abnormal N (%)	Not Done N (%)	Normal N (%)	Abnormal N (%)	Not Done N (%)
Head, Neck, Thyroid	32 (100)	0	0	30 (100)	0	0
Eyes, Ears, Nose, Throat	32 (100)	0	0	29 (96.7)	1 (3.3)	0
Chest, including Breasts	0	0	32 (100)	0	0	30 (100)
Lungs	32 (100)	0	0	29 (96.7)	1 (3.3)	0
Heart	32 (100)	0	0	29 (96.7)	1 (3.3)	0
Lymph Nodes	32 (100)	0	0	30 (100)	0	0
Abdomen	32 (100)	0	0	29 (96.7)	0	1 (3.3)
Anorectal	0	0	32 (100)	0	0	30 (100)
Genitourinary	0	0	32 (100)	1 (3.3)	0	29 (96.7)
Skin	32 (100)	0	0	28 (93.3)	2 (6.7)	0
Musculoskeletal	31 (96.9)	1 (3.1)	0	29 (96.7)	1 (3.3)	0
Neurologic	1 (3.1)	0	31 (96.9)	1 (3.3)	0	29 (96.7)
Other	0	2 (6.3)	0	0	0	0

Abstracted from Statistical Table 5.2.

[Sponsor's Table 4, Item 8, Vol. 1.55, p. 057]

Concomitants medications which continued into the study or were started during the study were not considered to interfere with the study results. They included such drugs as oxytocin to increase uterine tone, analgesics for post-operative pain and prophylactic antibiotics. All patients took preoperative antacids for aspiration prophylaxis.

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ON ORIGINAL

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Measurement:

The primary efficacy measurement is time to onset of sensory block adequate to carry out the cesarean section (extension of sensory block between T4-T6). The mean time to onset of sensory block was longer for levobupivacaine group. In the ITT population, "...there was a statistically significant difference between the two treatment groups ($p=0.023$); mean time to onset of sensory block was 9.8 and 6.4 minutes in the levobupivacaine and the bupivacaine groups, respectively (mean difference of 3.5 minutes)." In the per-protocol population, "there was no statistically significant difference between treatment groups ($p=0.076$); mean time to onset of sensory block was 8.2 and 6.4 minutes in the levobupivacaine and bupivacaine groups, respectively (mean difference of 1.8 minutes)".

"The 90% confidence intervals of the mean difference in time to onset of sensory block were 0.8 to 6.2 minutes for the Intent-to-Treat population and 0 to 3.7 minutes for the per-protocol population. For both populations, these boundaries are within the ± 7.26 minutes equivalence boundaries established per protocol. Accordingly, from a statistical basis, as well as from clinical measurements, the two treatment groups can be considered clinically comparable."

Of interest, however, is the chosen equivalence limits. Upon discussion with the reviewing statistician, an equivalence limit of ± 7.26 , which is $>100\%$ of the mean onset time of bupivacaine, allows levobupivacaine to take twice as long as bupivacaine to onset of sensory block and still be judged equivalent. In which case, they may not be clinically comparable.

Secondary Efficacy Measurement:

All analyses of secondary measurements were performed on the Intent-to-Treat population.

Time to Offset of Sensory Block

The statistical analysis of time to offset of sensory block was reported to show no statistical difference (p value note provided) between treatment groups with respect to time to T10 regression and time to complete offset of sensory block. The mean time to T10 regression was slightly longer for patients in the levobupivacaine group (329.2 minutes) versus the bupivacaine group (317.1 minutes). With the mean difference between them being 12.1 minutes, with a 95% CI of -29.1 to 53.3 (less than one hour apart).

The mean time to complete offset of sensory block was reported to be slightly longer for patients in the levobupivacaine treatment group (451.0 minutes) compared to patients in the bupivacaine group (428.1 minutes). With the mean difference between them being 22.9 minutes, with a 95% CI of -12.7 to 58.5 (less than one hour apart).

Table 20. Analysis of Secondary Efficacy Variables

Table 6 Time (Minutes) to Onset of T4-T6 Sensory Block: Intent-to-Treat Population

Variable	Levobupivacaine (N=32)	Bupivacaine (N=30)	p-value
Time to Onset of T4-T6 Sensory Block (Minutes)			
Mean \pm S.D.	9.8 \pm 8.02	6.4 \pm 3.96	0.023
Median	10.0	5.0	
Minimum	0	0	
Maximum	40	15	
Mean Difference	3.5		
95% Confidence Interval	(0.2, 6.7)		
90% Confidence Interval	(0.8, 6.2)		
T5 Bilateral Block Achieved			
Yes (N[%])	30 (93.8)	30 (100)	0.492
No (N[%])	2 (6.3)	0	

Abstracted from Statistical Table 7.1.

Table 7 Time (Minutes) to Onset of T4-T6 Sensory Block: Per-Protocol Population

Variable	Levobupivacaine (N=30)	Bupivacaine (N=30)	p-value
Time to Onset of T4-T6 Sensory Block (Minutes)			
Mean \pm S.D.	8.2 \pm 4.69	6.4 \pm 3.96	0.076
Median	10.0	5.0	
Minimum	0	0	
Maximum	16	15	
Mean Difference	1.8		
95% Confidence Interval	(-0.4, 4.1)		
90% Confidence Interval	(0.0, 3.7)		
T5 Bilateral Block Achieved			
Yes (N[%])	30 (100)	30 (100)	1.000
No (N[%])	0	0	

Abstracted from Statistical Table 7.2.

[Sponsor's Table 6 and 7, Item 8, Vol. 1.55, p. 053]

Table 21. Analysis of Secondary Efficacy Variable

Table 8 Time (Minutes) to Complete Offset of Sensory Block: Intent-to-Treat Population

Variable	Levobupivacaine (N=30)	Bupivacaine (N=30)	p-value
Mean \pm S.D.	451.0 \pm 68.90	428.1 \pm 68.97	0.257
Median	480.0	420.0	
Minimum	270	270	
Maximum	540	540	
Mean Difference	22.9		
95% Confidence Interval	(-12.7, 58.5)		

Abstracted from Statistical Table 8.

[Sponsor's Table 8, Item 8, Vol. 1.55, p. 054]

Time to Onset and Offset of Motor Block

The sponsor reports there to be no statistically significant differences between the two treatment groups, with respect to the motor block achieved. "Motor block was achieved for a slightly smaller percentage of patients in the levobupivacaine treatment group (81.3%) than in the bupivacaine group (93.3%). Six patients in the levobupivacaine treatment group (Patient Nos. 121, 137, 142, 169, 176, and 178), and two patients in the bupivacaine treatment group (Patient Nos. 141 and 179) did not achieve motor block. For analysis purposes, the times to onset of motor block for these patients were censored at the start time of surgery."

Time to Onset of Motor Block

With respect to the time of onset of motor block, the sponsor reports there to be no statistically significant difference. "Time to onset of motor block was slightly longer for patients in the levobupivacaine treatment group (mean of 17.2 minutes) compared to patients in the bupivacaine group (mean of 12.5 minutes). The mean difference between them was 4.7 minutes, with a 95% CI of -0.6 to 10.0 (10 minutes apart)."

Time to Offset of Motor Block

Finally, with respect to the time to offset of motor block, the sponsor reports there to be no statistically significant difference between groups. Time to offset of motor block was said to be shorter for the patients in the levobupivacaine group (mean 241.2 minutes) compared to the bupivacaine group (mean 265.2 minutes). The difference between them was reported to be -24.0 minutes, with a 95% CI of -68.3 to 20.3 (less than 70 minutes apart). Patients 121 and 169 who did not achieve adequate sensory block were excluded from this analysis.

Table 22. Analysis of Secondary Variable

Table 9 Time (Minutes) to Onset of Motor Block: Intent-to-Treat Population

Variable	Levobupivacaine (N=32)	Bupivacaine (N=30)	p-value
Time to Onset of Motor Block (Minutes)			
Mean ± S.D.	17.2 ± 12.16	12.5 ± 8.26	0.075
Median	15.0	15.0	
Minimum	0	0	
Maximum	60	30	
Mean Difference	4.7		
95% Confidence Interval	(-0.6, 10.0)		
Motor Block Achieved			
Yes (N(%))	26 (81.3)	28 (93.3)	0.258
No (N(%)) ¹	6 (18.8)	2 (6.7)	

Abstracted from Statistical Table 9, Data Listing 7.2.

¹ Six levobupivacaine patients (Patient Nos. 121, 137, 142, 169, 176, and 178), and two bupivacaine patients (Patient Nos. 141 and 179) did not achieve motor block. Time to surgery was the parameter used for these patients.

[Sponsor's Table 8, Item 8, Vol. 1.55, p. 055]

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ON ORIGINAL

The sponsor also evaluated motor block assessments over time and found that the "...majority of the assessment time points showed no statistically significant differences between treatment groups during pre-surgery and post-surgery assessments. The levobupivacaine treatment group showed less mean motor block at each of the following time points compared to the bupivacaine group. Statistically significant but clinically irrelevant differences were found at one of ten pre-surgery time points (5 minutes, on the left side, $p=0.038$), and at three of ten post-surgery time points (1 hour 30 minutes on the right side, $p=0.013$; 1 hour 30 minutes on the left side, $p=0.006$; 2 hours on the left side, $p=0.028$). The 2 hour time point on the right side approached, but did not reach statistical significance ($p=0.056$)."

Time to Onset of Anesthesia

The sponsor reports there to have been no statistically significant differences between treatment groups with respect to time to onset of anesthesia. "The mean time to onset of anesthesia was the same (0.5 minutes) for both the levobupivacaine and bupivacaine treatment groups. There was no difference between groups; the 95% CI was -0.9 to 0.8 minutes (less than one minute apart)."

Table 23. Analysis of Secondary Variable

Table 10 Time (Minutes) to Offset of Motor Block: Intent-to-Treat Population

Variable	Levobupivacaine (N=30)	Bupivacaine (N=30)	p-value
Mean \pm S.D.	241.2 \pm 89.59	265.2 \pm 81.70	0.446
Median	240.0	255.0	
Minimum	90	120	
Maximum	450	480	
Mean Difference	-24.0		
95% Confidence Interval	(-68.3, 20.3)		

Abstracted from Statistical Table 10.

[Sponsor's Table 9, Item 8, Vol. 1.55, p. 055]

Quality of Anesthesia

There were no statistically significant differences found between treatment groups at any of the patient assessed time points. Patients assessed their level of pain on a scale of 1=no pain to 100=very painful during surgery, post-delivery, and in the recovery room.

The sponsor computed an average pain score for each of the five pain assessments, and the mean pain assessments were compared between treatment groups. "Patients in the levobupivacaine treatment group had slightly less mean pain (mean of 0.64) compared to patients in the bupivacaine group (mean of 1.65). The mean difference between them was -1.0 points, with a 95% CI of -3.1 to 1.0 (less than 4 points apart)."

Muscle Relaxation

The following explanation is provided to explain the results of this analysis, "The anesthesiologist and obstetrician provided an overall assessment of muscle relaxation during surgery, on a scale of 0=worst to 4=best. Because only two scores (good and best) were seen for all of the patients in the anesthesiologist rated assessment, the Fisher's Exact test was used for this analysis (see Section 9.11). A t-test was used for the obstetrician rated assessment analysis."

"A statistically significant difference was found between treatment groups, with respect to the anesthesiologist rated muscle relaxation scores ($p=0.052$). The anesthesiologist rated muscle relaxation scores were lower in the levobupivacaine treatment group (mean of 3.8) compared to the bupivacaine group (mean of 4.0). The mean difference between them was -0.2 points, with a 95% CI of -0.3 to -0.0 (less than 0.4 points apart)."

"No statistically significant differences were found between treatment groups, with respect to the obstetrician rated muscle relaxation scores. The obstetrician rated muscle relaxation scores were slightly higher in the levobupivacaine treatment group (mean of 3.8) compared to the bupivacaine group (mean of 3.7). The mean difference between them was 0.1 points, with a 95% CI of -0.2 to 0.3 (less than 0.4 points apart). The inter-rated differences between the anesthesiologist and obstetrician rated muscle relaxation scores are not considered to be of much relevance clinically."

[Item 8, Vol. 1.55, p. 055-056]

Table 24. Analysis of Secondary Variable

Table 11 Overall Assessment of Muscle Relaxation: Intent-to-Treat Population

Variable	Levobupivacaine (N=32)	Bupivacaine (N=30)	p-value
Anesthesiologist Rating			
N	30	30	0.052
Mean ± S.D.	3.8 ± 0.38	4.0 ± 0.00	
Mean Difference	-0.2		
95% Confidence Interval	(-0.3, -0.0)		
0=worst	0	0	
1=poor	0	0	
2=fair	0	0	
3=good	5 (15.6)	0	
4=best	25 (78.1)	30 (100)	
missing	2 (6.3)	0	
Obstetrician Rating			
N	30	30	0.583
Mean ± S.D.	3.8 ± 0.41	3.7 ± 0.52	
Mean Difference	0.1		
95% Confidence Interval	(-0.2, 0.3)		
0=worst	0	0	
1=poor	0	0	
2=fair	0	1 (3.3)	
3=good	6 (18.8)	6 (20.0)	
4=best	24 (75.0)	23 (76.7)	
missing	2 (6.3)	0	

Abstracted from Statistical Table 14.

[Item 8, Vol. 1.55, p. 055-058]

Overall Assessments

The anesthesiologist and obstetrician provided an overall assessment of the quality of the sensory block during surgery, on a scale of 0 = failure to 2 = satisfactory. The sponsor reports there to have been no statistically significant differences between treatment groups. "The non-missing assessments of the quality of the block were rated the same (2=satisfactory) by both the anesthesiologist and the obstetrician in both treatment groups."

Table 25. Analysis of Secondary Variable

Table 12 Overall Assessment of Quality of the Block: Intent-to-Treat Population

Variable	Levobupivacaine (N=32)	Bupivacaine (N=30)
Anesthesiologist Rating		30
N	30	2.0 ± 0.00
Mean ± S.D.	2.0 ± 0.00	0.0
Mean Difference		(NE, NE)
95% Confidence Interval		
0=failure	0	0
1=unsatisfactory	0	0
2=satisfactory	30 (93.8)	30 (100)
missing	2 (6.3)	0
Obstetrician Rating		30
N	30	2.0 ± 0.00
Mean ± S.D.	2.0 ± 0.00	0.0
Mean Difference		(NE, NE)
95% Confidence Interval		
0=failure	0	0
1=unsatisfactory	0	0
2=satisfactory	30 (93.8)	30 (100)
missing	2 (6.3)	0

Abstracted from Statistical Table 15.

[Sponsor's Table 12, Item 8, Vol. 1.55, p. 059]

REVIEWER'S EFFICACY DISCUSSION

The primary efficacy measurement is time to onset of sensory block adequate to carry out the cesarean section (extension of sensory block between T4-T6). For the Intent-to-Treat population there was a statistically significant difference ($p=0.023$) between the two treatment groups - 0.5% levobupivacaine and 0.5% bupivacaine - in favor of bupivacaine (i.e., there was a longer time to onset with levobupivacaine).

Of interest is the chosen equivalence limits. Upon discussion with the reviewing statistician, an equivalence limit of ± 7.26 which is $> 100\%$ of the mean onset time of bupivacaine, this allows levobupivacaine to take twice as long as bupivacaine to onset of sensory block and still be judged equivalent.

With certainty, a drug with a slow onset time to sensory block is of little or no clinical usefulness in today's practice of anesthesiology.

The statistical analysis of the secondary efficacy variable, time to offset of sensory block was reported to show no statistical difference between treatment groups with respect to time to T10 regression and time to complete offset of sensory block.

Despite a slower onset of action, overall the clinical data shows that the product, 0.5% levobupivacaine, is effective when administered as an epidural infusion to obstetric patients undergoing a cesarean section. This conclusion is based upon the clear evidence that patients experienced some level of analgesia sufficient for cesarean section.

**APPEARS THIS WAY
ON ORIGINAL**

TUDY # 030276

PROTOCOL SYNOPSIS:

Title: "A Randomized Multicentre, Double-blind, Parallel, Group Study to Compare the Efficacy, Safety and Kinetics of 0.25% Levobupivacaine (s-enantiomer) with 0.25% Bupivacaine (racemic mixture) in Obstetric Patients Receiving Extradural Analgesia for Labour"

Primary Objective: "To compare the efficacy of 0.25% levobupivacaine with 0.25% bupivacaine, when used in extradural analgesia."

Secondary Objective: "To determine the plasma concentrations of levobupivacaine and bupivacaine following dosing with 0.25% levobupivacaine and 0.25% racemic bupivacaine, in a sample of 20 patients."

[Item 8, Vol. 1.58, p. 021]

**APPEARS THIS WAY
ON ORIGINAL**

Study Design:

The study is designed as a randomized, multi-center, double blind, 2-limb parallel group, analysis of the efficacy, safety and pharmacokinetics of 0.25% levobupivacaine versus 0.25% bupivacaine administered epidurally in obstetric patients in labor. 169 patients from three centers were randomized, 82 to the levobupivacaine group and 87 to the bupivacaine group. Center 1 recruited 47 patients, 73 by Center 2, and 49 by Center 4. Each center was assigned at least one block of randomization numbers for each parity status (primiparous and multiparous).

Eligible patients underwent a brief screening phase, followed by randomization stratified for parity, on an equal basis to receive either 0.25% levobupivacaine or 0.25% bupivacaine via epidural catheter for labor. They were then allocated the lowest number available on the randomization list at their assigned center.

Group I	0.25% levobupivacaine
Group II	0.25% bupivacaine

Eligible patients will be ASA Class I or II females between 18 and 40 years of age, of normal weight and height, at full-term normal pregnancy, i.e., ≥ 36 weeks gestational age, in cephalic presentation. Patients must have no prior history of diabetes or other systemic illness, previous cesarean section, pre-eclampsia, multiple pregnancies, or opioid use in the preceding 4 hours.

An unblinded person or pharmacist who assigned the next randomization number in sequence, according to whether the patient was a Primigravida or Multigravida, prepared the study drug. On the morning of surgery, an intravenous infusion of Hartmann's solution (500ml) was started followed by placement of an epidural catheter in compliance with the standard of care.

Following placement of the epidural catheter and injection of the 10 ml of study drug was injected (time 0 min). Initially, 3 ml of this 10 ml was injected as a test dose at a rate of 1 ml every 2 seconds. If after 5 minutes, there is no evidence of intravascular or subarachnoid injection, the remaining 7 ml of study drug was administered at 1 ml every 2 seconds.

Further 10 ml injections (, i.e., 'top-ups') were given at a rate of 1 ml every 2 seconds with an interval of 45 seconds after the first 5 ml, as needed, with a minimum time between 'top-ups' of 15 minutes. The maximum number of 'top-ups' was 8 and the maximum amount of drug given in a 4-hour period was 2 mg/kg.

Patients were asked to complete a verbal rating scale, (i.e., 0 = painful, 1 = aware but not painful, 2 = unaware) for 2 contractions before the epidural and thereafter at every contraction until the first "top-up" injection. After the first 'top-up' injection, they were then asked to rate their pain at every contraction until the second 'top-up' injection. The verbal rating scale was then recorded 15 min and 45 min post the second 'top-up' injection. Thereafter, the recordings were made every 30 minutes until the next 'top-up' and immediately prior to each subsequent 'top-up'. Please note Table 26. Schedule of Assessments below.

Duration of pain relief was defined as time from first painless contraction, (i.e., 'unaware' or 'aware but not painful') until the time of the second painful contraction. Reports of rectal pressure were not considered to be representative of a painful contraction.

Patients also recorded their pain using the VAS scale, (where 0 = no pain and 100 = severe pain), when the verbal rating score of 'painful' or 'unaware' was reported. The VAS scale was recorded in the exact same sequence as the verbal rating scale, see table below.

The extent of sensory block was measured using the blunt end of a 27 gauge dental needle at 5, 15, 30 and 60 minutes after the epidural injection, and at 30-minute intervals, thereafter, until the first 'top-up' injection. Subsequently, the recordings were made at 15 min and 45 min post the first 'top-up' injection and every 30 min thereafter, until post the second 'top-up' injection. The same sequence of recordings, i.e., 15min, 45 min, q30 min post 'top-up', continued until resolution of block post-delivery, see table below.

The investigator used the modified Bromage scale (0 = no paralysis and 3 = inability move lower limb) to assess level of motor blockade at 5, 15, 30 and 60 min, after the first 'top-up' injection. Assessments, thereafter, were conducted 15 min after subsequent 'top-ups' and at 30 min intervals unless a further 'top-up' was given. These assessments continued until full return of motor function. The investigator also gave an overall assessment of the quality of block 30 min after the first epidural injection and then 30 min after each 'top-up' using a 3 box categorical scale, where 0 = good 1 = fair and 2 = poor.

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Table 26. Schedule of Assessments

SCHEDULE OF ASSESSMENTS - STUDY NUMBER: ICR 030276

PROCEDURE	TIMEPOINT																	AT EACH CONTRACTION UNTIL 1st TOP-UP INJECTION	1st TOP-UP INJECTION	
	PRE-STUDY	2nd CONTRACTION PRIOR TO EXTRAURAL	CONTRACTION PRIOR TO EXTRAURAL	IMMEDIATELY PRIOR TO EXTRAURAL	1st EXTRAURAL INJECTION	5mins	7mins	8mins	10mins	15mins	20mins	25mins	30mins	45mins	60mins	30min intervals				
SCREENING ASSESSMENTS	X																			
PLASMA SAMPLES ***	X					X			X		X		X	X	X					
VERBAL RATING SCORE		X	X																	X
VERBAL APPOLOE SCALE		X	X																	X
ASSESSMENT OF SENSORY BLOCK							X		X			X		X	X					
ASSESSMENT OF MOTOR BLOCK							X		X			X		X	X					
OVERALL ASSESSMENT BY INVESTIGATOR													X							
FOETAL HEART RATE				X			X	X	X	X	X	X	X		X	X				
MATERNAL CARDIOVASCULAR ASSESSMENT				X			X	X	X	X	X	X	X		X	X				
TIME OF FIRST INJECTION																				
BIRTH WEIGHT																				
BLOOD FOR MATERNAL/FOETAL DRUG RATIOS																				
BLOOD FOR PO2 AND pH ***																				
APGAR SCORE																				
MNC SCORE																				
ADVERSE EVENTS																				
CONCOMITANT MEDICATIONS																				

KEY: *** At least 1 only

[Sponsor's Table, "Schedule of Assessments", Item 8, Vol. 1.58, p. 312]

TABLE 27. Schedule of Assessments (continued)

SCHEDULE OF ASSESSMENTS - STUDY NUMBER: ICR 030276

PROCEDURE	TIMEPOINT														POST DELIVERY	AT DISCHARGE	3-7 DAYS FOLLOWING DISCHARGE	
	1st TOP-UP INJECTION	15 min AFTER 1st TOP-UP	30min AFTER 1st TOP-UP	45min AFTER 1st TOP-UP	EVERY 30 min UNTIL NEXT TOP-UP	AT EACH CONTRACTION UNTIL 3rd TOP-UP INJECTION	2nd TOP-UP INJECTION	FROM 2nd TOP-UP ONWARDS					FURTHER TOP-UP INJECTIONS					
							15 min AFTER TOP-UP	30min AFTER TOP-UP	45min AFTER TOP-UP	EVERY 30 min UNTIL NEXT TOP-UP	IMMEDIATELY PRIOR TO EACH TOP-UP							
SCREENING ASSESSMENTS																		
PH SAMPLES																		
VERBAL RATING SCORE						X		X		X	X	X						
VERBAI ANALOGUE SCALE						X		X		X	X	X						
ASSESSMENT OF SENSORY BLOCK		X		X	X			X		X	X						X*	
ASSESSMENT OF MOTOR BLOCK		X		X	X			X		X	X						X*	
OVERALL ASSESSMENT BY INVESTIGATOR			X						X									
FETAL HEART RATE		X		X	X			X		X	X							
MATERNAL CARDIOVASCULAR ASSESSMENT		X		X	X			X		X	X							
TIME OF FIRST MICTURITION																	X	
BIRTH WEIGHT																	X	
BLOOD FOR MATERNAL/FETAL DRUG RATIOS																	X	
BLOOD FOR PO2 AND pH **																	X	
APGAR SCORE																	XX	
HAC SCORE																	XX	
ADVERSE EVENTS																	X	X
CONCOMITANT MEDICATIONS																	X*	X

KEY: * To be recorded until resolution of block ** At selected centres only

[Sponsor's Table, "Schedule of Assessments", Item 8, Vol. 1.58, p. 313]

STATISTICAL ANALYSIS

"The primary analysis population for efficacy in this study was the 'per-protocol' population. Confirmatory analysis on the primary efficacy variable only was performed using the 'intent-to-treat' population. The primary measure of efficacy was the duration of pain relief defined as the time from the first painless contraction (i.e., unaware or aware but not painful) until the time of the second successive painful contraction irrespective of whether or not a 'top-up' injection was given."

"The confirmatory efficacy analysis was to focus on the question of whether the difference in duration of pain relief between the two study drugs was within the pre-defined 'equivalence criteria', i.e., within ± 20 minutes."

"The statistical hypothesis behind this trial were as follows:

H_0 : The mean difference in duration of pain relief following the first epidural injection between the treatment groups is greater than 20 minutes.

H_1 : The mean difference in duration of pain relief following the first epidural injection between the treatment groups is less than 20 minutes."

"For both 'per-protocol' and 'intent-to-treat' populations, the following statistical analysis was to be performed:

"For those patients who experienced some pain relief (i.e., at least one contraction recorded as 'unaware' or 'aware but not painful' on the verbal rating scale), this response variable was to be analysed using analysis of variance (ANOVA) with terms for treatment, centre, parity (i.e., primigravida or multipara), treatment by parity interaction, treatment by centre interaction and other interaction terms. If any of the interaction terms were significant at the 10% level they were to be dropped from the model i.e., main and interaction effects were to be declared significant at the 5% and 10% levels respectively. Using the error variance from the ANOVA, comparison of the treatment LS Means (i.e., means adjusted for any imbalance in the design) were to be made using a Student's 't'-test. Estimates of treatment difference and associated 90% confidence interval were to be calculated. If the 90% confidence interval should lie within the acceptance range of -20 to 20 minutes then the two study drugs were to be judged equivalent. This is equivalent to the method of using two simultaneous one-sided tests to test the composite null hypothesis that the treatment difference is outside the equivalence margins versus the alternative that the treatment difference is within the limits."

"The residuals from this analysis were to be submitted to a Shapiro-Wilk test for normality and examined graphically to assess variance homogeneity. Any deviation from either assumption was to entail a re-analysis using an appropriate alternative transformation of the data e.g., log transformation. Furthermore, following examination of these data, non-parametric methods were to be used if the above methods were not considered appropriate."

"For the 'intent-to-treat' population, those patients who received a 'top-up' before experiencing their second painful contraction, the duration of pain relief was to be calculated from time of first painless contraction until the time of top-up as it was assumed that the decision to 'top-up' was made on clinical judgement that the pain relief was not satisfactory."

"The proportion of patients in each treatment group who did not experience pain relief (ie did not record any contractions as 'unaware' or 'aware but not painful' on the verbal rating scale) were to be compared using a Mantel-Haenszel test stratifying for parity. Breslow-Day statistics were to be used to test for a treatment by parity interaction. Main and interaction effects were to be declared significant at the 5% and 10% levels respectively. An estimate of the treatment difference and associated 95% confidence intervals were to be obtained."