

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20997**

**STATISTICAL REVIEW(S)**

# Statistical Review and Evaluation

## (SECONDARY REVIEW)

NDA 20-997

Name of drug: Chirocaine (levobupivacaine) injection

Applicant: Darwin Discovery

Indication: local anesthesia

Documents reviewed:

- primary statistical review by Yi Tsong, Ph.D.
- pharmacology review by Anwar Goheer, Ph.D.
- consultant's report by John P. DiMarco, M.D., Ph.D., 3 December 1998
- volumes 1.1, 1.96

Project manager: Susmita Samanta, M.D.

Medical officer: Monica Roberts, M.D.

Dates:

- received 27 April 1998
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- advisory committee 12 January 1999

Reviewer: Thomas Permutt

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### INTRODUCTION

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This is a secondary review to the primary statistical review of this application by Dr. Yi Tsong. I concur with Dr. Tsong's conclusion that the application is approvable from the standpoint of statistics. However, my view of the important issues in this application being somewhat different from Dr. Tsong's, I think it worthwhile to document it separately in this review.

Levobupivacaine is the levorotatory enantiomer of the chiral molecule bupivacaine. Racemic bupivacaine is an approved and widely used local anesthetic. Presumably, successful marketing of levobupivacaine would depend on its having some therapeutic advantage over bupivacaine. On the other hand, NDA approval does not require any demonstration of superiority. For the purpose of review, therefore, it is important to distinguish two aspects of the evidence submitted, which are not always clearly distinguished in the application. First, is there substantial evidence of superiority of levo- to racemic bupivacaine? Second, is there sufficient evidence of efficacy and safety simply to approve marketing of levobupivacaine?

Levobupivacaine has been studied in clinical trials in several of the usual indications for local anesthetics, usually with bupivacaine as an active control. The protocols for these studies mainly proposed primary statistical analyses designed, in form at least, to show equivalence. For example, in studies of epidural administration for surgery, time to onset was usually the primary numerical measure of outcome, and a prespecified difference (sometimes 10 minutes, sometimes 8 minutes) was to be regarded as clinically negligible. It was correct, I think, to specify primary statistical analyses, to allay any concerns about multiplicity with respect to any comparative findings that might arise. There were other, non-numerical outcomes, however, which might be viewed as primary from the standpoint of approvability. In cesarean section, for example, the primary question for approvability of the drug is whether levobupivacaine provided anesthesia of sufficient quality for the surgery to be carried out. It was, in almost all cases, with either treatment.

The general safety of levobupivacaine in clinical trials is discussed in Dr. Tsong's review, and I concur with his conclusion that it raises no special concern from a statistical standpoint. I believe the NDA contains ample, mainly nonstatistical, evidence of the efficacy of levobupivacaine in several anesthetic indications. Separate studies in different anesthetic techniques were necessary to gain descriptive information about the properties of levobupivacaine in each use, but, the mechanism of action being similar in all cases, these separate studies are also mutually supportive from the standpoint of evidence of efficacy. This review will very briefly discuss the trials in each indication. It will then turn to the very important question of the relative toxicity and potency of levobupivacaine and racemic bupivacaine.

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## EFFICACY

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### CESARIAN SECTION

Dr. Tsong reviews two studies (030632 and CS001) of levobupivacaine 0.5% and bupivacaine 0.5% for epidural anesthesia in elective cesarean section. In study 030632, thirty of 32 patients on levobupivacaine achieved "protocol proper block," as did 29 of 32 patients on bupivacaine. The protocol specified a primary statistical analysis comparing the time to onset of adequate block; it suggested without justification that a difference of less than 10 minutes could be considered unimportant. In fact the average times were both about 10 minutes, with a difference of one minute. In retrospect the standard for equivalence appears absurd, and no claim of equivalence is justified. However, levobupivacaine was clearly effective.

In study CS001, thirty of 32 patients on levobupivacaine achieved adequate block for cesarean section, as did all 32 patients on bupivacaine. Again the protocol specified a primary statistical analysis based on time to onset. In this case the mean times were 10 minutes for levobupivacaine and 6 minutes for bupivacaine. Again, a prespecified but unjustified criterion of equivalence (a difference of no more than 7.6 minutes) was met. Again, in retrospect, the criterion appears absurd, and no claim of equivalence is justified; but levobupivacaine was effective.

The draft labeling proposes to refer to these two trials as follows:

The numbers of patients refer incorrectly to the levobupivacaine and bupivacaine groups combined while seeming to refer only to Chirocaine. Except for that, the statements in this paragraph are in agreement with Dr. Tsong's review. They are appropriately descriptive of the effects of Chirocaine. The only comparison to bupivacaine, in the last sentence, is to the disadvantage of the test drug. The numbers should be rounded and should include measures of variability. I recommend the following language:

#### LABOR

Dr. Tsong reviews two studies (030276 and 030433) of levobupivacaine and bupivacaine for epidural control of labor pain. In study 030276, twenty of 68 "per-protocol" patients failed to achieve pain relief on levobupivacaine 0.25%, compared to 10 of 69 on bupivacaine 0.25%; this is a statistically significant difference. The primary statistical analysis concerned the duration of analgesia. A prespecified but unjustified criterion of 20 minutes' difference was met with 90% confidence, with analysis restricted to patients who achieved pain relief. However, given the lack of justification and the significant difference between groups in the proportion of patients who were included in this analysis, no claim of equivalence is appropriate.

Study 030433 compared levobupivacaine to bupivacaine in a complicated dose-ranging design. According to Dr. Tsong, the concentrations of levobupivacaine and bupivacaine needed to give pain relief were estimated to be approximately the same, but equivalence was not established.

The draft labeling does not refer to study 030433. It refers to study 030276 as follows:

0.25% Chirocaine was evaluated as intermittent injections via an epidural catheter in 137 patients during labor. The median duration of pain relief in patients receiving 0.25% Chirocaine was 49 minutes. Greater than 90% of patients achieved pain relief after the first top-up injection. The duration of pain relief data was equivalent in the 0.25% Chirocaine and 0.25% racemic bupivacaine treatment groups.

Again the number of patients is incorrect: Chirocaine was evaluated in 68 patients. The median duration of pain relief *in the subset with pain relief* was 49 minutes; this should be clarified. Precisely 90 percent (not "greater than 90%") of evaluable patients achieved pain relief after the first top-up injection. The last sentence, claiming equivalence, is not justified and should be deleted.

#### EPIDURAL CENTRAL BLOCK FOR SURGERY

The epidural central block technique was tested in lower limb surgery in study 006175 and in abdominal surgery in study CS005. In study 006175, levobupivacaine 0.5% and 0.75% were compared to bupivacaine 0.5%. All were effective. The protocol specified a primary analysis excluding patients who had general anesthesia, but an amendment after the blind was broken proposed including those patients. No statistically significant differences were observed with respect to the primary endpoint, duration of sensory block, in the analysis as originally specified, but in the revised analysis levobupivacaine 0.75% lasted significantly longer than the other two treatments. Numerically, levobupivacaine 0.5% was between the other two treatments.

Study CS005 compared levobupivacaine 0.75% and bupivacaine 0.75% in central block for abdominal surgery. The mean time to onset of sensory block (the primary statistical endpoint) was 10 minutes in both groups, and a prespecified but not well justified equivalence margin of 8 minutes was met with 95% confidence.

These trials are described in the draft labeling as follows:

Chirocaine concentrations of 0.50% and 0.75% administered by epidural injection were evaluated in 157 patients undergoing lower limb or major abdominal surgery. In patients having lower limb surgery, the duration of sensory block was similar in the Chirocaine and racemic bupivacaine groups. In patients having abdominal surgery, the mean time to onset of sensory block was 13.6 minutes. The mean duration of sensory block was 9.18 hours and the mean duration of motor block was 5.92 hours.

Again the sample size incorrectly includes patients not on Chirocaine. Whether the duration of sensory block was "similar" among the three groups depends on the analysis, and this statement does not seem to me to convey any useful information. The last sentence is also troublesome. Dr. Tsong gives the mean duration of sensory block as about 6 hours; the figure of 9.18 hours seems to be based on time to "complete regression." Obviously some confusion is possible, and the labeling must be clear. This is particularly important as sensory block without motor block would be a desirable characteristic of a local anesthetic agent in some circumstances, and this

sentence seems to invite such a claim. Possibly these statements can be made explicit enough to be useful, but I would recommend the following language:

*Chirocaine concentrations of 0.50% and 0.75% administered by epidural injection were evaluated in 85 patients undergoing lower limb or major abdominal surgery. In patients having abdominal surgery, the mean ( $\pm$  s.d.) time to onset of sensory block was  $14 \pm 6$  minutes.*

#### EPIDURAL CENTRAL BLOCK FOR PAIN MANAGEMENT

Dr. Tsong reviews four studies (0305475, CS004, CS006, 030742) of epidural levobupivacaine for central block in the management of postoperative pain. Study 0305475 compared three concentrations of levobupivacaine (0.0625%, 0.125%, 0.25%) after orthopedic surgery. The sponsor's primary analyses concerned the "survival" time until the first request for other analgesics. The analyses are somewhat complicated, so that the numerical results have no clear interpretation. There were, however, appropriate statistical tests of differences between treatments, and there were clearly statistically significant differences. These are evidence of the efficacy of levobupivacaine in epidural pain management.

Study CS004 was a factorial study comparing a combination of levobupivacaine and morphine to morphine alone and to levobupivacaine alone for pain following abdominal surgery. The primary comparison was of the combination to morphine alone with respect to request for rescue analgesia. The study failed to establish that levobupivacaine added to the efficacy of morphine.

Study CS006 was a similar factorial study of levobupivacaine and fentanyl in for pain following orthopedic surgery. The combination was better than either of the components in median time to rescue: about 9 hours for the combination, 8 hours for levobupivacaine alone and 7 hours for fentanyl alone. There were three withdrawals in the combination group, whose observations may have been incorrectly called censored in the statistical analysis. However, even if they had more conservatively been analyzed as if they had asked for rescue medication at the time of withdrawal, the combination group would still have been best.

Study 030742 tested combination therapy with clonidine for pain following hip replacement. Intravenous morphine delivered by a patient-controlled pump was used concomitantly, and the primary outcome was the amount of morphine consumed. The mean doses of morphine over 24 hours were 37 mg in the levobupivacaine group, 23 mg in the clonidine group and 14 mg in the combination group. The combination was significantly better than either of the components.

The draft labeling refers to the four studies in postoperative central block as follows:

Post-operative pain control was evaluated in 326 patients in one dose-ranging study and three studies assessing Chirocaine in combination with epidural morphine, fentanyl, or clonidine. Efficacy variables included the time to first request for rescue analgesia and patient-reported Visual Analogue Scale reports of the intensity of pain. The dose-ranging study evaluated Chirocaine in concentrations of 0.0625%, 0.125%, and 0.25% in patients undergoing orthopedic surgery. The mean time to first request for rescue analgesia was 8.11 hours in the 0.0625% Chirocaine group, 9.15 hours in the 0.125% Chirocaine group, and 16.66 hours in the 0.25% Chirocaine group. Patients in the 0.25% Chirocaine group reported less pain; however, the between group results for the two lower dose groups were similar.

The Chirocaine combination studies in post-operative pain management included: 0.25% Chirocaine in combination with 0.005% morphine in patients undergoing major abdominal surgery; 0.125% Chirocaine in combination with fentanyl and 0.125% Chirocaine in combination with clonidine 50 µg/hour in patients undergoing major orthopedic surgery. In these studies, the efficacy variable was time to the first request for rescue analgesia during the 24-hour epidural infusion period. In all studies, the combination treatment arm was clinically superior to treatment with Chirocaine or the combination agent alone.

As I said above, I do not think that "mean time to first request" is a meaningful descriptive statistic, even though significance tests based on it are appropriate. The reported pain was a secondary variable, and difficult to interpret in the presence of rescue medication. In the last sentence of the second paragraph, "clinically superior" appears to be a euphemism for (in one case) *not statistically significantly different*; this usage is not acceptable. I recommend:

*Post-operative pain control was evaluated in 258 patients in one dose-ranging study and two studies assessing Chirocaine in combination with epidural fentanyl or clonidine. The dose-ranging study evaluated Chirocaine in concentrations of 0.0625%, 0.125%, and 0.25% in patients undergoing orthopedic surgery; the highest concentration was significantly more effective than the other two. The Chirocaine combination studies in post-operative pain management tested 0.125% Chirocaine in combination with fentanyl and 0.125% Chirocaine in combination with clonidine 50 µg/hour in patients undergoing major orthopedic surgery. In these studies, the efficacy variable was time to the first request for rescue analgesia during the 24-hour epidural infusion period. In both studies, the combination treatment arm was superior to treatment with Chirocaine or the combination agent alone.*

#### PERIPHERAL NERVE BLOCK

A variety of peripheral nerve block techniques were studied: peribulbar block for ophthalmic surgery (030543, 030737), brachial plexus block for hand surgery (006154) and infiltration for pain following hernia repair (030428, 030721, CS007) or dental extraction (030700).

#### PERIBULBAR BLOCK

Studies 030543 and 030737 compared levobupivacaine and bupivacaine in ophthalmic surgery. Both treatments gave adequate block in almost all cases. The primary statistical analysis was of time to onset. No significant differences were found, but no equivalence analysis was proposed or conducted. The proposed labeling is descriptive and appears correct.

## BRACHIAL PLEXUS BLOCK

Study 006154 compared levobupivacaine 0.25%, levobupivacaine 0.5% and bupivacaine 0.5% in hand surgery. Again, almost all patients had an adequate block. Again, no significant differences were found with respect to time to onset, nor was equivalence established. The draft labeling is as follows:

A dose-ranging study of 0.25% and 0.50% Chirocaine was compared with 0.5% racemic bupivacaine in 74 patients receiving a brachial plexus block for elective surgery. The duration of sensory block was 17.3 hours in the 0.50% Chirocaine compared with 14.9 hours in the 0.5% racemic bupivacaine group.

The duration was a secondary outcome. It is not clear what the relevance of this particular comparison is. If it is necessary to say something about this study, it might be, *All 25, 24/25, and 22/23 patients in the three groups had adequate sensory block.* (One of the 74 patients had an "adverse reaction before dosing.")

## INFILTRATION

Two studies in adults (030428 and 030721) compared levobupivacaine and bupivacaine by infiltration for the control of postoperative pain after hernia repair. From the standpoint of the protocols, these were failed superiority studies. The protocols specified analyses aimed at showing that levobupivacaine was more effective than bupivacaine, but levobupivacaine turned out not to be significantly more effective. According to Dr. Tsong, the two studies also do not clearly show statistical equivalence of the two treatments.

Possibly, the protocols should not be taken too literally, and the studies of infiltration should be viewed like those of other techniques. In surgical anesthesia, levobupivacaine was effective enough to permit surgery, regardless of whether it was better, worse or about the same as bupivacaine. Perhaps a similar argument could be made for infiltration. A question of assay sensitivity arises, however. Most patients on either treatment in these studies were in pain. While the results with levobupivacaine and bupivacaine were broadly similar, it is not obvious to me (but it may be obvious to a medical reviewer) that the drugs were both effective, rather than both ineffective.

The draft labeling refers to these two studies as follows:

0.25% Chirocaine was evaluated in two clinical trials as infiltration anesthesia during surgery and for post-operative pain management in patients undergoing inguinal hernia repair. The intensity of pain experienced was reported by the patients using the Visual Analogue Scale (VAS); the normalized area under the VAS curve was similar for the Chirocaine and racemic bupivacaine treatment groups. The median time to first request for rescue analgesia was 9.33 hours following surgery.

In view of the reservations expressed above, I think the comparison of VAS scores is slightly overstated. The median time to rescue was a secondary variable and is not clearly interpretable; it is also not clear which study is being referred to, or if they have been pooled. I suggest:

*0.25% Chirocaine and racemic bupivacaine were evaluated in two clinical trials as infiltration anesthesia during surgery and for post-operative pain management in patients undergoing inguinal hernia repair. No clear differences between the treatments were seen.*

In addition, one study (CS007) compared levobupivacaine to placebo for the same indication in children from six months to 12 years old. Levobupivacaine was not statistically significantly better than placebo with respect to the primary endpoint (proportion of patients requiring rescue medication, 45 percent vs. 73 percent), but there were significant differences on some secondary endpoints.

It might be desirable to describe this pediatric study in labeling from the standpoint of safety, but no claim of efficacy should be allowed. Furthermore, this negative, placebo-controlled study, as well as that in dental pain, below, cast further doubt on the assay sensitivity of the active-controlled trials in this indication.

#### DENTAL EXTRACTION

Study 030700 compared levobupivacaine, lidocaine (lignocaine) and placebo for postoperative pain after extraction of wisdom teeth. Levobupivacaine was not statistically significantly better than placebo with respect to the primary endpoint. It is not appropriate to refer to this failed study in labeling (except as a failed study).

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#### RELATIVE POTENCY AND TOXICITY

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The limiting toxicities of bupivacaine are its effects on the central nervous system and on the heart. The label bears a box warning of "cardiac arrest with difficult resuscitation or death," recommending against the use of the 0.75% product in obstetrics. The applicant believes the dextrorotatory enantiomer of bupivacaine may be primarily responsible for these toxic effects, so that levobupivacaine might be safer. The question of how this putatively greater safety might be demonstrated was discussed at a meeting of the Anesthetic and Life Support Advisory Committee (24 March 1997) and in meetings between the sponsor and the division. At the pre-NDA meeting the sponsor indicated that the aim of the NDA was simply an approved product rather than a comparative claim. At that time the division advised the sponsor that such a claim would need to address issues of potency and toxicity together: if levobupivacaine were less toxic milligram for milligram but also less potent, better safety in use would not be clear.

The NDA does contain some information tending to indicate less toxicity of levo- than of racemic bupivacaine. It also contains other information tending to indicate roughly equal

potency. It does not, in my view, contain information sufficient to establish any claim of better safety in use.

The information on toxicity comes from animal studies, reviewed by Dr. Anwar Goheer; from electrocardiographic and hemodynamic measurements in three of the Phase III trials (CS005, 030721, 030632); and from two studies (004801, 012105) in volunteers. According to Dr. Tsong's review, no statistically significant differences were found between levo- and racemic bupivacaine in the Phase III trials except for a difference in the PR interval in Study 030662. In view of the multiplicity of comparisons, Dr. Tsong suggests that this finding is of doubtful significance, and I concur. In Study 004801, a crossover study in 14 volunteers, changes from baseline in several parameters were seen with both levobupivacaine and bupivacaine, but the treatments differed significantly from each other only with respect to the stroke index and the ejection fraction. Again Dr. Tsong suggests that these comparisons on secondary endpoints, in the context of many nonsignificant differences on primary and other secondary endpoints, are of questionable significance, and again I concur. Dr. John DiMarco, a cardiologist who reviewed this study as a consultant to FDA, also questions the clinical importance of these findings.

The draft labeling describes this study as follows:

Three clinical pharmacology studies have been conducted to evaluate the cardiovascular and central nervous system effects of Chirocaine. In one study, 14 healthy human volunteers received Chirocaine or racemic bupivacaine infusions intravenously until clinically significant CNS symptoms occurred (numbness of the tongue, light-headedness, tinnitus, dizziness, blurred vision, or muscle twitch). The mean dose at which CNS symptoms occurred was 56 mg for Chirocaine and 48 mg for racemic bupivacaine, though this difference did not reach statistical significance. At this dose, racemic bupivacaine induced statistically significant changes in several cardiovascular variables (stroke volume and acceleration index) compared with Chirocaine. Chirocaine had a statistically significant reduction in electrophysiological cardiotoxicity compared with racemic bupivacaine. Also, Chirocaine produced no statistically significant changes from baseline in any ECG intervals measured, whereas racemic bupivacaine produced statistically significant changes in PR interval and QTc interval.

I do not think this language is justified. The comment on "significant changes in several [two] cardiovascular variables" is misleading out of the context of the lack of significant changes in the primary and other secondary variables. The last sentence incorrectly suggests a difference between the two treatments because one is statistically significantly and the other nonsignificantly different from baseline, whereas in fact there was no significant difference *between the two treatments*. My recommendation is to delete this paragraph entirely, the study having failed to demonstrate the anticipated, statistically significant and clinically relevant differences.

A second study (012105) in 22 volunteers is also described in the draft labeling. This study was not reviewed by Dr. Tsong; the report was apparently not even included in the statistical section of the NDA. My remarks on this study are therefore based on a primary review of the study report in the clinical section (volume 1.96).

Study 012105 was a parallel-group study of the effects on electrocardiographic parameters of intravenous injection of levo- or racemic bupivacaine. In an open-label phase, patients were dosed with racemic bupivacaine until they experienced CNS symptoms. The same dose of either levo- or racemic bupivacaine was then given in a randomized, double-blind phase. The primary endpoints were prespecified: "maximum positive change from predose using the end of infusion, 5 min, 10 min, 15 min and 30 min timepoints for the QT dispersion and signal-averaged QRS values for each treatment." Dose was to be taken into account in the analysis by including a main effect with two levels (above or below 75 mg) as well as treatment and a treatment-by-dose interaction in an analysis of variance, but separate analyses by dose group were also reported. A protocol amendment provided for a repeated-measures analysis of the several timepoints in addition to the analysis based on the maximum positive change.

The mean ( $\pm$  s.d.) maximum (over time) changes from baseline in QT dispersion were  $9 \pm 14$  ms for bupivacaine and  $8 \pm 10$  ms for levobupivacaine. The difference was not statistically significant. The mean maximum changes in QRS duration were  $0.01 \pm 0.02$  s for bupivacaine and for levobupivacaine alike. No statistically significant differences between treatments in these parameters were observed in the stratified or the repeated-measures analyses, either.

Several secondary endpoints were also specified: "maximum positive change from predose using the end of infusion, 5 min, 10 min, 15 min and 30 min timepoints for the PR, QT and QTc durations for each treatment." A single statistically significant result in favor of levobupivacaine was found: the change in QTc was  $0.02 \pm 0.02$  s for bupivacaine and  $0.00 \pm 0.01$  s for levobupivacaine, in the higher dose group only, with a p-value of 0.02. There was also one significant difference in the opposite direction: at the 5 minute timepoint the change in PR interval was greater with levobupivacaine than with bupivacaine. The study report itself cautions against reliance on these statistically significant results as they were not adjusted for multiple comparisons. I concur.

The draft labeling is as follows:

A second cardiovascular study in healthy volunteers (Study 012105) compared the effects of Chirocaine and racemic bupivacaine given by intravenous infusion on electrocardiographic changes. Prior to dosing with study drug, each subject was given an infusion of lidocaine so that they would recognize the CNS symptoms that they would experience. The infusion was stopped when a subject reported any CNS symptom. After a suitable interval they were given an open label infusion of racemic bupivacaine until they experienced the same CNS side effects. The dose achieved with this racemic bupivacaine infusion became the dose given in the double-blind part of the study. The final dosing was either Chirocaine or racemic bupivacaine given in a double blind randomized fashion up to the dose that had been tolerated in the open label racemic bupivacaine infusion part of the protocol. The study size was powered on the difference in QT dispersion noted in protocol 004801. End points, in addition to QT dispersion, were PR interval, QRS duration, QT interval and QTc.

Twenty-two subjects were enrolled and completed all arms of the study. The doses tolerated ranged from 30 mg to 120 mg. A statistically significant difference ( $p=0.022$ ) was seen between Chirocaine and racemic bupivacaine with QTc in favor of Chirocaine in subjects who received more than 75 mg of either Chirocaine or racemic bupivacaine.

In Study 004801 a favorable but statistically nonsignificant difference in QT dispersion had been observed, and Study 012105 was specifically designed to find a difference in QT dispersion. It failed to do so. The reported significant difference is misleading out of the context of many negative results, including all the results on the primary endpoints. Again, I recommend deletion of this questionably reliable information.

As to potency, most of the Phase III trials discussed above compared levobupivacaine and bupivacaine at equal doses. For the most part, no significant differences were found, but the evidence of equivalence was also weak. In one study (006175) where levobupivacaine 0.75% was compared to bupivacaine 0.5%, there was no clear evidence that levobupivacaine 0.75% was more effective.

Levo- and racemic bupivacaine have qualitatively similar pharmacologic and toxic effects. At equal doses there is evidence from animal studies, and very weak indications from human studies, that levobupivacaine may be less toxic; some of the animal data suggest that equitoxic doses of the two drugs might differ by around 30 percent. On the other hand, there is little evidence that equipotent doses may not also differ by 30 percent. In Study 006175, levobupivacaine at a 50% higher dose than bupivacaine was not clearly more effective.

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**CONCLUSIONS**

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The NDA contains substantial evidence that levobupivacaine is a safe and effective local anesthetic, comparable to bupivacaine. The application is approvable from the standpoint of statistics. No claim of relative safety of levo- to racemic bupivacaine appears to be statistically justified.

/S/ 1/4/99

Thomas Permutt, Ph.D.  
Mathematical Statistician (Team Leader)

/S/ -

4/4/99

Concur: Michael Welch, Ph.D.  
Acting Deputy Director, Division of Biometrics II

# NDA Statistical Review and Evaluation

NDA#: 20-997  
Drug Product: Chirocaine™ (Levobupivacaine injection) 0.25%, 0.5%, 0.75%  
Sponsor: Darwin Discovery Limited  
Indications: Surgical Analgesia and pain control  
Received Date: April 27, 1998  
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Ken Nolan

CSO:  
Complete Date:  
Medical Reviewer: Monica Roberts, MD  
Primary Reviewer: Yi Tsong, PhD  
Secondary Reviewer: Thomas J. Permutt, PhD

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## **Introduction**

NDA 20997 was submitted for the application of approval of Chirocaine™ (Levobupivacaine injection) 0.25%, 0.5%, 0.75% as new drug for the indication of surgical analgesia and pain control. The drug product was sponsored by Darwin Discovery Limited. The statistical section of the application consists of the following NDA volumes, 1.1, and 1.107-1.157, BS-1, BS-2. The materials contained in these volumes are the information of all the randomized, double blinded, parallel arms phase III efficacy trials including Studies 030632, CS-001, 030276, 030433, 006175, CS-005, 030475, CS-004, CS-006, 030742, 030428, 030721, 006154, 030543, 030737, 030700, and CS-007.

In addition, this document contains also the review of Study 012105 and Study 004801. Study 012105 was a special analysis of ECG data from four phase I and III studies for the cardiovascular effect of the treatment. Study 004801, was a pharmacological study designed for the evaluation comparison of the cardiovascular effects of racemic Bupivacaine and S-bupivacaine in 14 healthy male.

In this NDA, the statistical term of 2-limbs or 3-limbs in stead of the traditional 2-arms or 3-arms were used in all studies. The same terms were used in this review for the consistency.

**APPEARS THIS WAY  
ON ORIGINAL**

## I. Obstetric Studies (Phase III Comparative Studies)

Study #	Design	Dose	Number of treated (safety)	Age mean	Sex(M/F) Race (W,B,O)	Indication
<b>Obstetric Studies</b>						
030632	Dblind / random / parallel / 2 centers	Levobupivacaine -150mg 0.5% Bupivacaine - 150mg 0.5%	67 (64)	29.6 (18-40)	0/69 69,0,0	Elective cesarean cessation / Epidural injection
CS 001	Dblind / random / parallel	Levobupivacaine -150 mg 0.5% Bupivacaine - 150mg 0.5%	63 (62)	33.8 (23-40)	0/63 51, 5, 7	Elective cesarean cessation / Epidural injection
030276	Dblind / random / parallel	Levobupivacaine - up to 200 mg 0.25% Bupivacaine - 200mg 0.25%	169 (162)	27.3 (18-40)	0/169 160, 0, 9	Pain control for labor / Epidural injection
030433	Dblind / random / parallel	Levobupivacaine -(variable dose) Bupivacaine - (variable dose)	73 (73)	26.4 (16-37)	0/73 68, 1, 4	Pain control for labor / Epidural injection

### I.1 Study 030632

I.1.a. Study Design: Randomized, double blind, parallel group (Levobupivacaine -150mg 0.5% and Bupivacaine - 150mg 0.5%) study conducted in two centers in the United Kingdom.

#### I.1.b. Efficacy Endpoints:

Primary measure - Anesthesia adequate to carry out the Cesarean section was measured at 0, 2, 5, 10, 15, 20, 25, 30, 45 and 60 min or until a block of T4-T6 was achieved and then at 30 min until the block had progressed to T10. The time to onset of protocol adequate sensory block for surgery was the primary measure of efficacy.

#### Secondary Endpoints -

Quality of Anesthesia recorded by patients during surgery at the time of skin incision; at the time of abdominal opening; at the time of uterine incision and in the recovery room. The pain was recorded using a 100-mm visual analogue scale. Motor block assessment continued every 30 minutes until the return of full motor power. Muscle relaxation assessment of muscle relaxation was recorded during the procedure. Overall assessment of the quality of block using a categorical scale recorded after surgery.

Safety Evaluations - A 12-lead ECG, a 3-lead ECG, heart rate, systolic blood pressure, diastolic blood pressure were measured every 30 minutes in the recovery room.

I.1.c. Population for Analysis: Primary efficacy variable was analyzed using the 'intent-to-treat' population. The secondary efficacy endpoints were analyzed using the "per-protocol" population. All patients received medication was included in the summary of safety data. Patient did not receive study medication or with unsuccessful extradural injection were excluded from the 'intent-to-treat' analysis. The 'per-protocol' population included all patient in the 'intent-to treat' population except those who did not complete the study at all full-term pregnancy or who had a history of any disease or disorders likely to impact on the efficacy of the study

medication or received any non-study medications which might impact on the efficacy of the study.

#### **I.1.d. Efficacy analysis:**

##### **Methods:**

##### The confirmatory efficacy analysis:

The study was designed to test whether the mean difference between the new treatment group and the active control group in time to onset of protocol adequate sensory block for surgery was within a pre-defined 'equivalence limit',  $D_0$ . The statistical hypotheses to be tested are

$$H_0: E(\text{mean difference in time to onset between the two groups}) \geq D_0$$

$$H_a: E(\text{mean difference in time to onset between the two groups}) < D_0$$

The 'equivalence limit',  $D_0$ , was pre-specified at 10 minutes by the sponsor without any specific justification.

The sample size of the study was determined to be 30 evaluable patients per group. With this sample size, the study would have 99% power to reject the null hypothesis based on a 2-sided t-test approach at 10% type error rate with standard deviation, 9.7 min, of time to onset as estimated in a previous parallel clinical trial study.

##### The secondary efficacy response variables:

- i. Time to onset of 'clinically adequate injection block'
- ii. Time to onset of sensory block
- iii. Time to sensory block offset
- iv. Proportion of patients recording motor block prior to surgery
- v. Proportion of patients responding at each grade of motor block
- vi. Time to offset of motor block
- vii. Average quality of analgesia
- viii. Muscle relaxation
- ix. Overall assessment of block
- x. Proportion of patients requiring extra 10 ml of study drug during surgery

All of the secondary endpoints except iv, v, viii, ix and x were analyzed with 'per-protocol' population only. The two treatments were judged equivalence if the 90% confidence interval for the difference lies within  $\pm 10\%$  of the Bupivacaine group mean. For the rest secondary endpoints, logit model test was used to test for the regular null hypothesis of equal proportions.

##### The safety variables:

The safety variables were adverse events, vital signs, neonatal monitoring including infant Apgar and NAC scores. There were no formal statistical analysis performed.

##### **Results:**

##### Subject disposition and withdrawals:

The treatment allocation was described in Table I.1.1.

**Table I.1.1 Treatment allocation**

Center	Entered and randomized	Levobupivacaine Group			Bupivacaine Group		
		entered	withdrawal	Complete	entered	withdrawal	Complete
1	29	15	1	14	14	0	14
2	40	20	3	17	20	1	19
Total	69	35	4	31	34	1	33

**Demographic data:**

The two treatment groups were similar in age, height, weight, obstetric history details, medical/surgery history and medications in safety population, intent-to-treat population and in pre-protocol population.

**Table I.1.2 Sample Means (standard Deviation) of Baseline Demographics of the two treatments (Modified from NDA Tables 4.1-4.3 pp.132-134, vol. 107)**

Variable	Levobupivacaine			Bupivacaine		
	Center 1	Center 2	All	Center 1	Center 2	All
Safety Population N	15	18	33	14	20	34
Age (years)	27.7 (6.5)	29.5 (5.5)	28.7 (5.9)	31.1 (6.1)	29.9 (3.8)	30.4 (4.8)
Height (cm)	162.8 (5.4)	160.5 (5.3)	161.5 (5.4)	161.3 (8.2)	160.3 (5.5)	160.7 (6.6)
Weight (Kg)	72.6 (12.8)	78.1 (10.2)	75.6 (11.6)	74.6 (11.9)	80.5 (12.8)	78.1 (12.6)
Caucasian/Hispanic/Asian	15/0/0	17/1/0	32/1/0	13/0/1	20/0/0	33/0/1
Intent-to-treat Population N	14	17	31	14	19	33
Age (years)	28.2 (6.4)	29.5 (5.7)	28.9 (6.0)	31.1 (6.1)	29.8 (3.9)	30.4 (4.9)
Height (cm)	162.4 (5.4)	160.5 (5.5)	161.4 (5.5)	161.3 (8.2)	160.0 (5.5)	160.5 (6.7)
Weight (Kg)	73.0 (13.2)	78.4 (10.4)	76.0 (11.8)	74.6 (11.9)	80.0 (12.9)	77.7 (12.6)
Caucasian/Hispanic/Asian	14/0/0	16/1/0	31/1/0	13/0/1	19/0/0	32/0/1
Per-protocol population N	14	17	31	12	19	31
Age (years)	28.2 (6.4)	29.5 (5.7)	28.9 (6.0)	32.5 (5.5)	29.8 (3.9)	30.8 (4.7)
Height (cm)	162.4 (5.4)	160.5 (5.5)	161.4 (5.5)	159.6 (6.6)	160.0 (5.5)	159.8 (5.8)
Weight (Kg)	73.0 (13.2)	78.4 (10.4)	76.0 (11.8)	73.9 (12.3)	79.9 (12.9)	77.6 (12.8)
Caucasian/Hispanic/Asian	14/0/0	16/1/0	31/1/0	11/0/1	19/0/0	30/0/1

**Efficacy Endpoints:**

There were 5 patients (2/32 in Levobupivacaine group and 3/32 in Bupivacaine group) failed to achieve protocol proper block. There was no significant difference between the two treatment groups.

**Primary efficacy endpoint -**

(ITT population): The mean times to onset of protocol adequate sensory block of the two

treatments were 10.2 min (Levobupivacaine) and 9.0 min (Bupivacaine) respectively. The least square difference was 1.6 min with 95% CI (calculated by statistical reviewer) of (-2.01, 5.21).

(Per-protocol population): The least square difference was 1.6 min with 95% CI (calculated by statistical reviewer) of (-1.92, 5.21).

#### Secondary endpoints -

Time to onset of clinically adequate block - The mean times were 12.6 min (Levobupivacaine) and 11.4 min (Bupivacaine) respectively. The least square difference was 1.5 with 95% CI (recalculated by statistical reviewer) of (-1.69, 4.69).

Time to offset of sensory block - The mean times were 485.9 min (Levobupivacaine) and 462.7 min (Bupivacaine) respectively. The least square mean difference was 19.0 with 95% CI (recalculated by statistical reviewer) of (-53.2, 91.2).

Time to onset of sensory block - Eighty seven percent of patients recorded 0 onset time in both groups. There were 3 patients in each group recorded 2 minute. The difference between the two groups was not statistically significant.

Time to offset of motor block - The mean times were 241.9 min (Levobupivacaine) and 171.8 min (Bupivacaine) respectively. The least square mean difference was 48.0 with 95% CI (recalculated by statistical reviewer) of (10.0, 90.0).

Average quality of analgesia - The median values were 2.33 (Levobupivacaine) and 0.25 (Bupivacaine) respectively. The difference was 2.08 with 95% CI (recalculated by statistical reviewer) of (-0.21, 4.52).

Proportion of patients recording motor block prior to surgery - Forty-two percent (13/31) of Levobupivacaine patients and twenty-six percent (8/31) of the patients treated with Bupivacaine had no record of any motor block prior to surgery. The odds ratio of having recorded motor block was 2.03 with 95% CI (calculated by Statistical reviewer) of (0.66, 6.23). The difference in percentage was not statistically significant.

Maximum grade of motor block reported - Patients in Levobupivacaine group reported more lower grade of motor block than patients in Bupivacaine (29% vs. 10% in grade 0, 48% vs. 48% in grade 1, 13% vs. 26% in grade 2 and 10% vs. 16% in grade 3 respectively). The difference in proportion is statistically significant ( $p=0.037$ , Wald statistic).

Muscle relaxation - In anesthetists assessment, patients in Levobupivacaine group had slighter worse muscle relaxation than those in the Bupivacaine group (6% vs. 10% rated fair, 87% vs. 71% rated good, and 6% vs. 19% rated best). The difference was not statistically significant. Similar results were also obtained in obstetrician's assessment (3% vs. 0% rated poor, 3% vs. 13% rated fair, 87% vs. 74% rated good and 6% vs. 13% rated best). The difference was not statistically significant.

Overall assessment of block - There was no statistically significance between the two treatment groups in anesthetist's (55% vs. 77% rated satisfactory) and obstetrician's (87% vs. 90%)

assessment of block:

Proportion of patients requiring extra 5 ml of study drug during surgery - The proportions were 10% in Levobupivacaine group and 3% in Bupivacaine group. The difference was not statistically significant.

Table I.1.4. Treatment means and difference of the endpoints (modified from NDA Tables 8.2.1 to 15.1, pp. 150-164, vol. 107)

Endpoint	Levobupivacaine Mean (std)	Bupivacaine Mean(std)	LSMean Difference (95% CI)
Intent-to-treat population (excluding the patients failed to achieve protocol block)			
Time to onset of protocol adequate block	10.2 (7.2), n=29	8.7 (6.6), n=30	1.6 (-2.01, 5.21)
Per-protocol population			
Time to onset of protocol block	10.2 (7.2), n=29	9.0 (6.7), n=28	1.6 (-1.92, 5.12)
Time to onset of clinically adequate block	12.6 (6.8), n=31	11.4 (6.0), n=31	1.5 (-1.69, 4.69)
Time to offset of sensory block	485.9 (142.8), n=29	462.7 (137.8), n=29	19.0 (-53.2, 91.2)
Time to offset of motor block	241.9 (131.2) n=22	171.8 (70.4) n=28	48.0 (10.0, 90.0)
Average quality of analgesia median	2.33; n=31	0.25; n=31	2.08 (-0.21, 4.52)

**Safety variables -**

There was no standout difference in adverse event reported in the two treatment groups. The most common adverse events were hypotension (57.6% and 79.4% for Levobupivacaine and Bupivacaine respectively), nausea (33.3% and 41.2% for Levobupivacaine and Bupivacaine respectively), and anemia (36.4% and 23.5% for Levobupivacaine and Bupivacaine respectively).

There was no standout difference in the vital signs or in neonatal monitoring between the two treatment groups.

**I.1.f. The Reviewer's Comments and conclusions**

The efficacy of Levobupivacaine was demonstrated by the high percentage of patients recorded protocol adequate sensory block. However, the decision on equivalence was not clear. This reviewer agrees with the sponsor's analysis in general except a 95% confidence intervals for the difference are presented in this review instead of the 90% confidence intervals presented by sponsor.

**Primary endpoint:** This study showed that in "intent-to-treat" population, the treatment difference between Levobupivacaine and Bupivacaine patients in time to onset of protocol defined block was 1.6 minutes with 95% confidence interval of (-1.92, 5.21). Levobupivacaine was shown to be equivalent to Bupivacaine by showing that the difference was less than 10 minute, the equivalent limit pre-specified by sponsor. Compared with the observed mean value, this limit was large. This reviewer would rely on the medical reviewer's judgement on the appropriateness of the limit. The same conclusion can be drawn for the 'per-protocol'

population.

**The secondary endpoints:**

The mean time to offset of sensory block was 485.9 and 462.7 minutes for the Levobupivacaine and Bupivacaine respectively. The difference was 19.0 minutes with 95% CI of (-53.2, 91.2). It failed the equivalence criterion proposed by the sponsor.

The mean time to offset of motor block was 241.9 minutes and 171.8 minutes for Levobupivacaine and Bupivacaine respectively. The difference was 48.00 minutes (95% CI=(10.00, 90.00)). The median value of average quality of analgesia was 2.33 (Levobupivacaine) and 0.25 (Bupivacaine) respectively. The difference was 2.08 with 95% CI of (-0.21, 4.52).

Forty-two percent (13/31) of Levobupivacaine patients and twenty-six percent (8/31) of Bupivacaine patients recorded any motor block prior to surgery. The Levo/Bupi odds ratio of having recorded motor block was 2.03 with 95% CI of (0.66, 6.23). The difference in percentage was not statistically significant. However, it was not statistical evidence for equivalence.

Patients in the Levobupivacaine group reported more lower grade of motor block than patients in the Bupivacaine group (29% vs. 10% in grade 0, 48% vs. 48% in grade 1, 13% vs. 26% in grade 2 and 10% vs. 16% in grade 3 respectively). The difference in proportion was statistically significant ( $p=0.037$ , Wald statistic).

In anesthetists assessment, patients in the Levobupivacaine group had slighter worse muscle relaxation than those in the Bupivacaine group (6% vs. 10% rated fair, 87% vs. 71% rated good, and 6% vs. 19% rated best). The difference was not statistically significant. Similar results were also obtained in obstetrician's assessment (3% vs. 0% rated poor, 3% vs. 13% rated fair, 87% vs. 74% rated good and 6% vs. 13% rated best). The difference was not statistically significant. There was no equivalence assessment made for this endpoint.

There were no statistically significance between the two treatment groups in anesthetist's (55% vs. 77% rated satisfactory) and obstetrician's (87% vs. 90%) assessment of block. This result should not be interpreted as equivalence.

The proportion of patients requiring extra 5 ml of study drug during surgery was 10% in Levobupivacaine group and 3% in Bupivacaine group respectively. The difference was not statistically significant. There was no equivalence assessment made.

**Safety:** There was no standout difference in safety variables between Levobupivacaine and Bupivacaine patients.

## **1.2 Study CS001**

**1.2.a. Study Design:** Randomized, double blind, parallel group (Levobupivacaine -150mg 0.5% and Bupivacaine - 150mg 0.5%) study conducted in single center in the United Kingdom.

**1.2.b. Efficacy Endpoints:**

Primary measure – The time to onset of T4-T6 sensory block protocol adequate to carry out surgery was the primary measure of efficacy.

Secondary endpoints included, time to onset of sensory block, time to onset of anesthesia, quality of anesthesia, time to onset and offset of motor block, muscle Relaxation, overall assessment at the end of study, and maternal and neonatal blood levels following study drug use at the time of delivery.

**1.2.c. Population for Analysis:**

Primary efficacy variable was analyzed using the 'intent-to-treat' population. All patients received medication was included in the summary of safety data. Patients who did not receive study medication or patients with unsuccessful extradural injection were excluded from the 'intent-to-treat' analysis. Patients who was not eligible for the 'intent-to treat' population, patients who was not at full-term pregnancy, patients who had a history of any disease or disorders likely to impact on the efficacy of the study medication, or patients who received any non-study medications which might impact on the efficacy of the study were excluded from the 'per-protocol' population.

**1.2.d. Efficacy analysis:**

**Methods:**

The time to onset or offset are estimated by using a product limit survival analysis with the ITT population.

**The confirmatory efficacy analysis:**

The primary efficacy endpoint was tested to show whether the mean difference between the new treatment group and the active control group in time to onset of block protocol adequate for surgery within a pre-defined 'equivalence criteria',  $D_0$ . The statistical hypotheses to be tested are

$$H_0: E(\text{mean difference in time to onset between the two groups}) \geq D_0$$

$$H_a: E(\text{mean difference in time to onset between the two groups}) < D_0$$

Determination of 'equivalence criteria',  $D_0$  – The non-inferiority limit is set at 7.26 minutes. It is pre-defined by the sponsor based on the assumption that the common onset time is 17 minutes with a standard deviation of 9.7 minutes. A difference in time to onset of less than 7.6 minutes was considered by sponsor to be clinically meaningless.

Sample size – The sample size is determined to be 30 evaluable patients per group. With this sample size, the study would have 80% power to reject the null hypothesis based on a 1-sided t-test approach at 5% type error rate.

The secondary efficacy response variables included, time to offset of sensory block, time to onset of motor block, time to offset of motor block, time to onset of anesthesia, average quality of analgesia, muscle relaxation and overall assessment of block.

**Results:**

Subject disposition and withdrawals –

Table I.2:1 Patients Disposition (NDA, Table 2 page 048, Vol. 109)

Patients	Levobupivacaine N (%)	Bupivacaine N (%)	All Patients N (%)
Randomized	33 (100)	32 (100)	65 (100)
Withdrawn Prior to Randomized Treatment	1 (3.0)	1 (3.1)	2 (3.1)
Safety Population	32 (97.0)	31 (96.9)	63 (96.6)
Received Study Drug but No Post-Baseline Efficacy Evaluation	0	1 (3.1)	1 (1.5)
ITT Population	32 (97.0)	30 (93.8)	62 (95.4)
Pre-Protocol Population	30 (90.9)	30 (93.8)	60 (92.3)
Non-Protocol Evaluable	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)

Demographic and Baseline Characteristics:

The sample consisted of 80.6% Caucasian, 8.1% Black, 8.1% Asian and 3.2 % Hispanic and Others. Patients had a mean age of 33.7 with standard deviation of 3.26 years, 24.2% with primagravida and 75.8% with multipara obstetric history, 71.0% with Cesarean experience. There was no significant difference between the two groups.

The time to onset and offset of the sensory block, motor block anesthesia were estimated for the ITT and pre-protocol populations using survival data analysis.

Primary Efficacy Endpoint:

Two of the Levobupivacaine patients failed to achieve the T5 bilateral sensory block, but the difference in the proportion of achieving the T5 block between the two groups were not statistically significant. Levobupivacaine group (9.8 min) had longer mean time to onset of sensory block than the Bupivacaine group (6.4 min). The mean difference was 3.5 min with a 95% confidence interval of the difference (0.2, 6.7) and p-value=0.023. But the CI was narrow enough to lie within the equivalence limits pre-specified by the sponsor.

Secondary Efficacy Endpoints:

Time to offset of sensory block – The difference in time to offset of sensory block was not statistically significant between the means of the two groups (p=0.257, t-test). The difference in mean time to offset was less than one hour (95% CI=(-12.7, 58.5))(See Table I.2.2).

Time to T-10 regression – The mean time to T-10 regression was slightly longer for the Levobupivacaine group. The mean difference was 12.1 minutes with a 95% CI=(-29.1, 53.3).

Time to onset of motor block – The difference in time to onset of motor block was not statistically significant between the means of the two groups (p=0.075, t-test). The difference in mean time was no more than 10 minutes (95% CI=(-0.6, 10.0)).

Time to offset of motor block – The difference in time to offset of motor block was not statistically significant between the means of the two groups (p=0.446, t-test). The difference in mean time was less than 68.3 minutes (95% CI=(-68.3, 0.3)).

Time to onset of anesthesia – The difference in time to onset of anesthesia was not statistically

significant between the means of the two groups (p=0.942, t-test). The difference in mean time was less than 1 minute (95% CI=(-0.9, 0.8)).

Table I.2.2 The mean values and the 95% confidence intervals of difference of means of the efficacy endpoints (modified from NDA Tables 6-11, pp.053-058, Vol. 109)

Endpoints	Treatment mean (std)		Difference (95% CI) t-dist, p-value
	Levobupivacaine	Bupivacaine	
Time to onset of sensory block (ITT)	9.8 (8.02)	6.4 (3.96)	3.4 (0.2, 6.7), 0.029
Time to onset of sensory block (pre-protocol)	8.2 (4.96)	6.4 (3.96)	1.8 (-0.4, 4.1), 0.076
Time to offset of sensory block (ITT)	451.0 (68.90)	428.1 (68.97)	22.9 (-12.7, 58.5), 0.257
Time to onset of motor block (ITT)	17.2 (12.16)	12.5 (8.26)	4.7 (-0.6, 10.0), 0.075
Time to offset of motor block (ITT)	241.2 (89.59)	265.2 (81.70)	-24.0 (-68.3, 0.3), 0.446
Time to onset of anesthesia (ITT)	0.5 (1.59)	0.5 (1.63)	0.0 (-0.9, 0.8), 0.442

Quality of anesthesia – Patients treated with Levobupivacaine had lower pain score than the patients treated with Bupivacaine in all events. There was no statistically significant difference in mean value between the two treatments in each event (i.e. the 95% confidence interval of mean treatment difference contained 0) (Table I.2.3),

Table I.2.3 The mean values and the 95% confidence intervals of difference of means of pain scores (1=no pain to 100=very painful) (modified from NDA Table 13.1-13.2 pp. 413-416, Vol. 109)

Event	Treatment mean (std)		Difference (95% CI) t-dist
	Levobupivacaine	Bupivacaine	
Skin incision	0.0	0.0	0.0
Abdominal incision	0.53 (2.285)	1.03 (5.474)	-0.5 (-2.7, 1.7)
Urine incision	0.56 (2.284)	1.04 (5.474)	-0.5 (-2.7, 1.7)
Urine manipulation post-delivery	1.25 (4.481)	5.58 (17.858)	-4.3 (-11.1, 2.4)
Recovery Room	0.83 (2.890)	0.61 (2.211)	0.2 (-1.1, 1.6)
Average pain assessment	0.64 (1.770)	1.65 (5.277)	-1.0 (-3.1, 1.0)

Muscle Relaxation – Patients treated with the two treatments had similar mean score of muscle relaxation. The difference was not statistically significant (i.e. the 95% confidence interval of difference contained 0) (Table I.2.4).

Table I.2.4 The mean values and the 95% confidence intervals of difference of means of muscle relaxation rated by anesthesiologist and obstetrician (0=worst to 4=best) (modified from NDA Table 11, page 058 Vol. 109)

Event	Treatment mean (std)		Difference, (95% CI) t-dist, p-value
	Levobupivacaine	Bupivacaine	
Anesthesiologist Rating	3.8 (0.38)	4.0 (0.00)	-0.2 (-0.3, -0.0), 0.052
Obstetrician Rating	3.8 (0.41)	3.7 (0.52)	0.1 (-0.2, 0.3), 0.583

Overall Assessment – The two treatment groups had the same mean overall score of overall assessment rated either by the anesthesiologist or obstetrician (Table I.2.5).

Table I.2.5 The mean values and the 95% confidence intervals of difference of means of overall assessment (0=failure to 2=satisfactory) made by anesthesiologist and obstetrician (0=worst to 4=best) (modified from NDA Table 11, page 058 Vol. 109)

Event	Treatment mean (std)		Difference (95% CI) t-dist
	Levobupivacaine	Bupivacaine	
Anesthesiologist Rating	2.0 (0.00)	2.0 (0.00)	NE
Obstetrician Rating	2.0 (0.00)	2.0 (0.00)	NE

### Safety Assessment:

There was no death in the study. All patients had at least one maternal event. There was 1 patient with severe adverse event (psychiatric disorders) in the Levobupivacaine group compared with 2 (central and peripheral nervous system disorders, and gastrointestinal system disorders) in the Bupivacaine group. There was one patient with serious adverse event (intravascular absorption of local anesthesia) that led to discontinuation of study in the Bupivacaine group. There were 26 patients with neonatal adverse event in the Levobupivacaine group compared with 27 patients in the Bupivacaine group. One patient in the Levobupivacaine group had severe adverse event (respiratory system disorders). There were 8 patients with serious adverse event in the Levobupivacaine group compared with 6 in the Bupivacaine group. None of the difference was of any statistical significance (Table I.2.6).

Table I.2.6 Adverse events (based on NDA Table 20.1-20.2, page 467-468, vol. 109)

Event N (%)	All patients N=63	0.5% Levobupivacaine N=32	0.5% Bupivacaine N=31	Diff. In proportion	p-value
<b>Maternal adverse events</b>					
With at least one event	63 (100.0)	32 (100.0)	31 (100.0)	0	
Moderate or severe adverse event	3 (4.8)	1 (3.1)	2 (6.5)	-0.032	0.633
Serious adverse events	1 (1.6)	0 (0.0)	1 (3.2)	-0.032	0.492
Discontinued	1 (1.6)	0 (0.0)	1 (3.2)	-0.032	0.492
<b>Neonatal adverse events</b>					
With at least one event	53 (84.1)	26 (81.3)	27 (87.1)	-0.068	0.732
Moderate or severe adverse event	1 (1.6)	1 (3.1)	0 (0.0)	0.031	1.000
Serious adverse events	14 (22.2)	8 (25.0)	6 (19.4)	0.056	0.763
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0	

There were 27 (84.4%) study drug related adverse events experienced by patients treated with Levobupivacaine compared with 30 (96.8%) in the Bupivacaine group. The most frequent events were hypotension (24 in Levobupivacaine and 30 in Bupivacaine), gastrointestinal (8 in Levobupivacaine and 9 in Bupivacaine):

Maternal vital signs monitored during surgery were summarized in NDA Tables 18.1-18.4 (page 423-464, vol. 109). There was no evidence of difference between the two groups.

Electrocardiograms were obtained at screening and pre-surgery. Several non-clinically significant abnormalities were found in both groups. The ECG results were not statistically significant at any time between the two groups. There was no evidence of difference between the groups in infant Aspar scores recorded at 1 and 5 minute post-delivery.

### 1.2.f. Reviewer's Comments and Conclusions

Study CS-001 was designed to establish treatment efficacy by comparing Levobupivacaine treatment with an active control treatment, Bupivacaine. The critical equivalence limit was selected to make the active control as a surrogate for placebo and also to represent a limit by which any difference between the two treatments would be medically meaningless. The sponsor based on a previous study, 7.26 minutes of time from receiving treatment to onset of sensory block, determined the limit. The limit of 7.26 min was larger than the mean time for the Bupivacaine group. The upper 95% confidence limit of the difference indicated that it would not rule out that the mean time of Levobupivacaine was twice as long as the mean time for the Bupivacaine group. The validity of such a limit is to be judged under medical consideration.

Given that the limit was valid, the study was designed with sufficient power to reject the null hypothesis that the difference in mean time to onset of sensory block between the two treatments is greater than 7.26 minutes. Based on the "intent-to-treat" population, data collected in this trial provided evidence on efficacy equivalence by rejecting the null hypothesis.

There was no significant difference between the two treatments for all secondary efficacy endpoints. However, failing to show significant difference between the two treatments provided no confirmatory strength in statistics for the evidence of equivalence of the new treatment.

There was no evidence of difference in safety profiles between 0.5% Levobupivacaine and Bupivacaine of the equal dose.

### **1.3 Study 030276**

**1.3.a. Study Design:** A Randomized, double blind, parallel group (Levobupivacaine -150mg 0.25% and Bupivacaine - 150mg 0.25%) study conducted in three centers in the United Kingdom.

#### **1.3.b. Efficacy and Safety Variables:**

Primary efficacy measures were the duration of analgesia, which was defined as the time from first painless contraction until the time of the second successful painless contraction.

Secondary Endpoints included onset of analgesia (determined by the first report of painless contraction), visual analogue pain scale, sensor block, motor block, overall Assessment at the end of study.

Measures of safety included cardiovascular measures including heart rate, diastolic blood pressure, fetal/neonatal monitoring, duration of first and second stages of labor and the mode of delivery, and adverse events

#### **1.3.c. Population for Analysis:**

Primary efficacy variable was analyzed using the "intent-to-treat" population. All patients received medication was included in the summary of safety data.

Patient did not receive study medication or patients with unsuccessful extradural injection were excluded from the "intent-to-treat" analysis. The "per-protocol" population would include all patients eligible for the "intent-to treat" population except those that were not at all full-term pregnancy, or had a history of any disease or disorders likely to impact on the efficacy of the study medication, or patients that received any non-study medications which might impact on the efficacy of the study.

#### **1.3.d. Efficacy analysis:**

##### **Methods:**

The confirmatory efficacy analysis was as follow,

The primary efficacy analysis was to test whether the mean difference in duration of pain relief following the first extradural injection between the treatment groups was within a pre-defined equivalence limit,  $D_0$ . The statistical hypotheses to be tested are

$H_0: E(\text{mean difference in duration between the two groups}) \geq D_0$

$H_0: E(\text{mean difference in duration between the two groups}) < D_0$

The equivalence limit,  $D_0$ , was set at 20 minutes as given by the sponsor in the study protocol. There was no medical or statistical explanation for the selection of the equivalence limit.

The sample size was determined to be 75 patients per group. With this sample size, the study would have 90% power to reject the null hypothesis based on a 2-sided t-test approach at 5% type error rate.

The secondary efficacy response variables included the secondary efficacy variables analyzed were, duration of pain relief following each "top-up" dose, time to pain relief, area under the curve (AUC) of Visual Analogue Score for all assessment following each dose of study drug, and proportion of patient recorded each grade of motor block.

### Results:

Subject disposition and withdrawals - the randomized, intent-to-treat, per-protocol, safety and primary efficacy analysis populations were defined in Table I.3.1.

Table I.3.1 Patient disposition for efficacy and safety analysis (NDA Tables 2.1-3.3, pp. 72-89, vol. 112)

Status	Treatment		Total
	Levobupivacaine	Bupivacaine	
Randomized (Safety Population)	82	87	169
Center #1	23	24	47
Center #2	35	38	73
Center #4	24	25	49
Intent-to-Treat Population	76	86	162
Technical Failure	6	1	7
Per-protocol Population	68	69	137
Received Opioids	2	2	4
<2 painful contractions	5	13	18
No painful contraction	1	2	3
Primary Efficacy Population	20	10	30
Did Not Achieve Pain Relief	48	59	107

### Demographic and Baseline Characteristics:

In the "safety" population of 169 patients, the Levobupivacaine patients had a mean age of 27.1 years, mean height of 162.7 cm, and mean weight of 76.67 kg. The Bupivacaine patients had a mean age of 27.4 years, mean weight of 75.63 kg, and mean height of 161.9 cm. There was no significant difference between the two groups.

Similar demographic characteristics were observed in the "intent-to-treat" and "per-protocol" populations.

The treatment groups were similar with respect to obstetric and medical history, and concomitant medications

**Primary Efficacy Endpoint:**

Percentage of patients failed to experience pain relief: Levobupivacaine treated patients had significantly lower percentage of patients experienced pain relief than Bupivacaine treated patients in either "intent-to-treat" population (73.3% vs. 86.9%, Odds ratio=0.37, p=0.018) and in "per-protocol" population (70.6% vs. 85.5%, Odds ratio=0.40, p=0.039)(Table 1.3.2).

The primary efficacy endpoint, duration of pain relief, was analyzed in two ways. One analysis was carried out by including patients with no pain relief (duration = 0). Since the duration of pain relief had high frequency at 0 when the patients with no pain relief were included in the analysis, comparison between the treatment was carried out using a nonparametric method. The median duration of pain relief was primarily analyzed using the "intent-to-treat" population, although the results using the "per-protocol" population were similar. The median duration was shorter in Levobupivacaine treated patients (43 min with 75 patients) than of the Bupivacaine treated patients (53 min with 84 patients). The difference in mean duration was statistically significant (p=0.005 using Wilcoxon model)(Table 1.3.3). On the other hand, the lower limit of the 90% confidence interval of the difference in mean using Mann-Whitney test was less than - 23 minute, which was lower than the equivalence limit pre-specified in the protocol.

When excluding the patients who experienced no pain relief, patients treated with Levobupivacaine had a median duration of 53 minutes (of 53 patients with pain relief only) which was shorter than the median duration of 58 minutes (of 73 patients with pain relief only) using the "intent-to-treat" population. The difference in mean of duration was not statistically significant and the 90% confidence interval lied within the equivalence limits. However, this results was conditioned on excluding a significantly larger portion in Levobupivacaine treated group than in Bupivacaine treated group of those patients who experienced no pain relief (Table 1.3.3).

Similar results were also found when using the "per-protocol" population.

Table 1.3.2 Percentage of patients experienced pain relief for the first injection (Based on NDA Tables 8.1.1 to 8.2.1, pp.123-127, vol. 112)

	Treatment		Odds Ratio (L/B) 95% CI p-value
	Levobupivacaine	Bupivacaine	
"Intent-to-treat" population n (%)	55 (73.3)	73 (86.9)	0.37 (0.16, 0.84) 0.018 (Wald Stat)
"Per-Protocol" Population n (%)	48 (70.6)	59 (85.5)	0.40 (0.17, 0.96) 0.039

**Table I.3.3 Median duration of pain relief (min) of the 1<sup>st</sup> injection (Based on NDA Tables 9.1.1 to 9.2.2, pp. 127-130, vol. 112)**

	Treatment median (n)		Diff in mean duration (90% CI) p-value of GLM
	Levobupivacaine	Bupivacaine	
<b>Including patients with no pain relief (1<sup>st</sup> Injection)</b>			
"Intent-to-treat" population median (n)	43 (75)	53 (84)	-13, (-23, -3) 0.005
"Per-Protocol" Population (Evaluable patients) median (n)	32 (68)	45 (69)	-10, (-21, 0) 0.024
<b>Excluding patients with no pain relief (1<sup>st</sup> Injection)</b>			
"Intent-to-treat" population median (n)	53 (54)	58 (73)	-6, (-14, 2) 0.16
"Per-Protocol" Population (Evaluable patients) median (n)	49 (48)	51 (59)	-4 (-13, 6) 0.38

**Secondary Efficacy Endpoints**

Analysis of secondary efficacy endpoints was carried out using "per-protocol" patients. Due to the lack of normality, duration of pain relief and time to onset of pain relief were analyzed using nonparametric methods. The results were as follow,

1. There were 60 evaluable patients in Levobupivacaine group, 6 of them did not experienced pain relief after the 1<sup>st</sup> top-off. The median duration of this group was 73 minutes including patients with no pain relief and 82 minutes excluding patients with no pain relief. There were 52 evaluable patients in Bupivacaine group, 2 of them did not experienced pain relief after the 1<sup>st</sup> top-off. The difference in the percentage of patients failed to have pain relief was not significant. The median duration of this group was 75 minutes including patients with no pain relief and 76 minutes excluding patients with no pain relief. The difference in-mean was not statistically significant (p=0.62 including patients with no pain relief and p=0.80 excluding patients with no pain relief using Generalized Wilcoxon model). The 90% confidence intervals of mean difference were (-21, 8) and (-15, 12) of groups including and excluding patients with no pain relief respectively (Table I.3.4).
2. The time to onset of pain relief was analyzed excluding the patients experienced no pain relief in the per-protocol population. The median time was equal in both treatment group (m=12, 90 CI=(-2, 2)) at the first injection. The median was 7 minutes in the Levobupivacaine group and 6 minutes in the Bupivacaine group (Table I.3.4).
3. Normalized area under the VAS score vs. time curve, AUC, was estimated with the following rules:
  - a. Where the patient was asleep or had recorded a "painless" contraction on VAS, the missing VAS was replaced by zero.
  - b. When all VAS scores were missing, no attempt was made to replace them.
  - c. Missing VAS scores due to missing recording at the start of the second stage of

- labor were ignored.
- d. Based on the lognormal assumption of AUC, geometric mean was estimated.

The geometric least square mean AUC adjusted for imbalance and the baseline VAS value, was 22.7 mm in the Levobupivacaine group and 15.8 mm in the Bupivacaine group at the 1<sup>st</sup> injection. The treatment difference was statistically significant (p=0.018 ANOVA). The ratio of the means was 1.44 (Levobupivacaine/Bupivacaine) with the 90% CI being (1.12, 1.85). The geometric least square mean AUC after the 1<sup>st</sup> top-off was 7.3 mm in the Levobupivacaine group and 6.6 mm in the Bupivacaine group. This difference was not statistically significant.

4. Distribution of recorded grade of motor block - Patients recorded the grade of motor block with the following instruction,  
0 = no paralysis, full flexion of knees and ankles, 1 = inability to raise extended leg, can move knees, 2 = inability to flex knees, can flex ankles, 3 = inability to move lower limb.

There was no statistical difference in the distribution of recorded grade of motor block between the two groups (see Table I.3.5)

5. Sensory block and overall quality of analgesia – There was no formal statistical analysis of the two endpoints.

Table I.3.4 Duration of pain relief (min) after the 1<sup>st</sup> top-off, time to onset of pain relief and time normalized area under the VAS score vs. time curve (AUC) (per-protocol population with evaluable patients) (Based on NDA Tables 9.1.1 to 9.2.2, pp. 127-130, vol. 112)

Efficacy Endpoint	Treatment median (n)		Diff in mean (90% CI) p-value of GLM
	Levobupivacaine	Bupivacaine	
<b>Duration of Pain Relief after the 1<sup>st</sup> top-off</b>			
"Per-Protocol" Population Including patients with no pain relief median (n)	73 (60)	75 (52)	-6, (-21, 8) 0.62
"Per-Protocol" Population Excluding patients with no pain relief median (n)	82 (54)	76 (50)	-1 (-15, 12) 0.80
<b>Time to Onset of Pain Relief</b>			
"Per-Protocol" Population Excluding patients with no pain relief 1 <sup>st</sup> Injection median (n)	12 (48)	12 (59)	0 (-2, 2) 0.91
"Per-Protocol" Population Excluding patients with no pain relief 1 <sup>st</sup> Top-off median (n)	7 (54)	6 (50)	1 (0, 3) 0.14
<b>VAS AUC</b>			
"Per-Protocol" Population Excluding patients with no pain relief 1 <sup>st</sup> Injection Geometric mean/LSMean (n)	18.46*/22.7 ** (68)	12.41/15.8 (69)	1.44 *** (1.12, 1.85) 0.018
"Per-Protocol" Population Excluding patients with no pain relief 1 <sup>st</sup> Top-off Geometric mean/LSMean (n)	7.0/7.3 (60)	4.79/6.6 (52)	1.09 (0.82, 1.45) 0.60

\*: Geometric mean

\*\* : Geometric least Square mean adjusted for imbalance and baseline AUC

\*\*\*: Ratio of LSMeans (Levobupivacaine/Bupivacaine)

Table I.3.5 Recorded grade of motor block (based on NDA Table 12, page 149, vol. 112)

Time	Grade	Treatment		Odds Ratio (95% CI) p-value
		0.25% Levobupivacaine	0.25% Bupivacaine	
1 <sup>st</sup> Injection n (%)	0	57 (84)	57 (85)	0.95 (0.38, 2.33) 0.90
	1	10 (15)	12 (17)	
	2	1 (1)	0 (0)	
	All Patients	68 (100)	69 (100)	
1 <sup>st</sup> Top-off n (%)	0	38 (66)	33 (63)	0.90 (0.40, 2.01) 0.80
	1	19 (33)	18 (35)	
	2	1 (2)	1 (2)	
	All Patients	58 (100)	52 (100)	

### Safety Evaluation

- 1 Extent of exposure – The distribution of number of injection of the two groups were given in NDA Table VI, page 72, vol. 112. The most frequent number of injections was 2, 3 and 4 in both groups. There was no evidence of difference between the two groups.
- 2 Serious adverse events – There were 71 serious adverse events experience by 62 patients, 30 in Levobupivacaine group and 41 in the Bupivacaine group. Thirty-seven cesarean sections and twenty-eight admissions to Special Care Baby Unit were reported. Seven of the events were classified as “unknown” relationship to the study drugs. The rest were classified as “non-related” to the study drugs. There was no evidence of difference between the two groups.
- 3 Adverse events – There were 79% of Levobupivacaine patients and 66% of Bupivacaine patients experienced any adverse events. The difference was statistically significant with p-value equaled to 0.045 using likelihood ratio chi-square test. The Levobupivacaine -to-Bupivacaine relative risk of experiencing adverse event was 1.21 with 95% confidence interval being (1.002, 1.461). The most common events were general disorders (20.7% in Levobupivacaine and 19.5% in Bupivacaine), fetal disorders (30.5% in Levobupivacaine and 24.1% in Bupivacaine), neonatal and infancy disorders (23.2% in Levobupivacaine and 28.7% in Bupivacaine), red blood cell disorder (28.0% in Levobupivacaine and 24.1% in Bupivacaine) and reproductive disorders (31.7% in Levobupivacaine and 26.4% in Bupivacaine).
- 4 Adverse events occurred during the therapy phase - There were 30.5% of Levobupivacaine patients and 19.5% Bupivacaine patients experienced adverse events during the therapy phase. The difference was not statistically significant (p=0.100, likelihood ratio chi-square test). The Levobupivacaine-to-Bupivacaine relative risk was 1.56 with the 95% confidence interval being (0.912, 2.670).
- 5 Vital signs, physical findings and other safety variables – There was no formal statistical analysis of vital signs, post delivery neonatal monitoring, and duration of labor and umbilical measurements. From the summarized data, there was no evidence of any difference between the two groups.

### I.3.e. Reviewer's comments and conclusions:

This reviewer had the following comments and conclusions:

#### Primary efficacy -

1. There was significantly higher percentage of Levobupivacaine patients failed to experience pain relief than the Bupivacaine group (26.7% vs. 13.1% with p-value = 0.018). The similar result was shown in the “pre-protocol” population.

2. When primary endpoint was analyzed by including all patients with no pain relief (duration=0), the Levobupivacaine group had a significantly shorter mean duration of pain relief than the Bupivacaine group ( $p=0.005$  using the Wilcoxon model). The result was similar using "per-protocol" population. In addition, the lower limit of the 90% confidence interval of the difference (-23 minutes) was lower than the equivalence limit pre-specified by the sponsor.
3. The null hypothesis of equivalence testing was rejected when the data was reanalyzed by excluding the patients with no pain relief. However, due to the fact that the proportion of patients failed to experience pain relief was statistically significant, result of this second analysis was biased in favor of equivalence.

#### **Secondary efficacy endpoints –**

1. There was evidence to support the equivalence in the secondary endpoints of duration of pain after the 1<sup>st</sup> top-off if excluding patients with no pain relief. But it failed when the patients with no pain relief were included in the analysis.
2. There was no statistical significant difference in the median time to onset of pain relief following the 1<sup>st</sup> injection. The analysis was not carried out as an equivalence testing.
3. Levobupivacaine group had significantly greater normalized area under the VAS score vs. time curve following the 1<sup>st</sup> injection, than Bupivacaine group with  $p=0.018$  using ANOVA. The difference was not statistically significant after the 1<sup>st</sup> top-off.
4. There was no statistical significance in the distribution of the recorded grade of motor block between the two treatments.

#### **Safety evaluation –**

1. Levobupivacaine patients had higher relative risk than Bupivacaine patients did in experiencing adverse events in the study and during the therapy phase. The relative risk were significantly higher than 1 with  $p=0.045$  in the study. However, the difference was not statistically significant during the therapy phase.
2. There was no evidence of difference between the treatments in extent of exposure, serious adverse events, vital signs, physical findings and other safety variables.

### **1.4 Study 030433**

**1.4.a Study Objective:** The aim of the study was to describe the dose response relationship for Levobupivacaine when used in obstetric patients receiving extradural analgesia during labor. The dose response relationship was determined by using onset of action, duration of action and quality of analgesia data to calculate the minimum local analgesic concentration (MLAC) of extradural Levobupivacaine. MLAC was defined as the effective concentration in 50% of patients ( $EC_{50}$ ).

**1.4.b Study Design:** It was a randomized, double blind, parallel group study conducted in single center in the United Kingdom. The concentration of study drug for each patient was determined by the response of the previous patient to a higher or lower concentration using the technique of double blind, up-down sequentially allocation. Patients were randomized to receive either Levobupivacaine or Bupivacaine. Additional Patient were recruited to replace all "rejects" and "withdrawals" and recruitment were continued until there were 30 patients, made up of "effectives" and "ineffectives", in each group.

#### **I.4.c. Efficacy Endpoints:**

Primary measure was pain of contraction, which was measured with visual analogue score using a 100 mm scale (0='no pain' to 100='worst pain possible'). Pain recorded immediately before the extradural injection was administered and at 5, 10, 15, 20, 25, 30, 45, 60 and 75 minutes after the injection or until an outcome was reached. Outcomes were defined:

'Effective' = the score was  $\leq 10$  mm during contraction within 30 min of the study drug injection and without 'Entonox' being used;

'Ineffective' = the score was  $> 10$  mm at all times during the 30 min following the study drug injection or until rescue medication was administered, whichever was sooner;

'Reject' = the score was  $> 10$  mm at all times during the 30 min following the study drug injection and did not respond to rescue medication or a score of

'Withdrawal' = patient was withdrawn from the study.

MLAC was estimated based on patients with either 'effective' or 'ineffective' outcomes.

Secondary Endpoints included extent of sensory block, and assessment of motor block. Safety was monitored throughout the study. Adverse events were recorded

#### **I.4.d. Population for Analysis:**

The calculation of the minimum local analgesic concentration (MLAC) was to be carried out using all evaluable patients (i.e. those patients defined as 'effective' or 'ineffective'). The analysis of secondary endpoints was performed on all patients received study medication.

#### **I.4.e. Efficacy and safety analysis:**

##### **Methods:**

The time to onset or offset was estimated by using a product limit survival analysis with the ITT population.

##### The confirmatory efficacy analysis:

The primary efficacy endpoint was tested to show whether the true difference in MLAC is not greater than a pre-defined 'equivalence limit',  $D_0$ . The statistical hypotheses to be tested are

$$H_0: E (\text{mean difference in MLAC between the two groups}) \geq D_0$$

$$H_0: E (\text{mean difference in MLAC between the two groups}) < D_0$$

Equivalence limit,  $D_0$  was pre-specified at 0.017%. It was 25% of the MLAC for Bupivacaine estimated in a previous study with similar study group.

The sample size was determined to be 30 evaluable patients per group. With this sample size, the study would have 90% power to reject the null hypothesis based on a 2-sided t-test approach at 5% type error rate.

**Secondary Endpoints** – There was no specific equivalence hypothesis defined and the study was not designed with proper sample size for testing the secondary endpoints.

**Results:**

**Subject disposition and withdrawals –**

**Table I.4.1 Patients Disposition (NDA, Table 2, page 048, Vol. 109)**

Patients	Levobupivacaine N (%)	Bupivacaine N (%)	All Patients N (%)
Randomized	37 (100)	36 (100)	73 (100)
Protocol Violation	2 (5.4)	4 (11.1)	6 (8.2)
Failure to reach outcome	3 (8.1)	1 (2.8)	4 (5.5)
Other violation	2 (5.4)	1 (2.8)	3 (4.1)
Evaluable	30 (81)	30 (83.5)	60 (82)

**Demographic and Baseline Characteristics:**

The 73 patients received study drugs were of mean age 26.4 years, mean weight 162.8 and mean height 76.4 kg. The demographic characteristics were similar between the two groups.

The similarity between the two groups was also shown in obstetric history, medical history, and usage of concomitant medications.

**Primary Efficacy Endpoint:**

The difference of MLAC between the two groups was 0.002. The 95% confidence interval of difference in MLAC, (-0.031, 0.035) failed to lie within (-0.017, 0.017), the equivalence limit. The null hypothesis was not rejected to establish the equivalence of the two treatments. The relative potency was estimated as 0.98 (95% CI=(0.58, 1.38)).

**Table I.4.2 the mean values and the 95% confidence intervals of difference of mean (median) of the efficacy endpoints (modified from NDA Tables K.1, pp.384, Vol. 116)**

Endpoints	Treatment		Difference (95% CI) t-dist
	Levobupivacaine	Bupivacaine	
MLAC (all evaluable patients) median (95%CI)	0.083 (0.065, 0.101)	0.081 (0.054, 0.109)	0.002 (-0.031, 0.035)

**Secondary Efficacy Endpoints:**

No full analysis carried out for the secondary endpoints. A similar pattern in sensory block was seen in the evaluable patient population of the two treatments. At 30 minutes post dose, there were 2 patients suffered from some paralysis of the left side and 1 patient suffered from paralysis of the right side of the Levobupivacaine group, compared with 3 patients suffered from paralysis of the left side and 3 patients suffered from paralysis of the right side in the Bupivacaine group. The difference was not statistically significant. The data were summarized in NDA Tables L1.1 .1 to L1.2.2 for sensory block assessment, Tables L1.3 – L1.4 for motor block, pp. 419-428; vol. 113.

**Safety Analysis:**

Twenty ml of study medication was administered over a 5-minute period. Both study drugs were administered at various concentrations. Levobupivacaine was administered with a concentration ranged from \_\_\_\_\_% and Bupivacaine was administered with a range from \_\_\_\_\_%.

**Adverse events** – A total of 25 adverse events experienced by 18 patients (49%) in the Levobupivacaine group and a total of 35 adverse events experienced by 21 patients (58%) in the Bupivacaine group. Similar profile was observed in both treatment groups except adverse events of gastrointestinal system disorders. There was 1 patient (2.7%) with gastrointestinal system disorders in the Levobupivacaine group compared with 6 patients (16.7%) in the Bupivacaine group. Seven patients treated with Levobupivacaine had drug related adverse events compared with 9 patients in the Bupivacaine group. The most frequent adverse event the patients experienced were fetal disorders (5 (13.5%) in Levobupivacaine group and 5 (13.9%) in Bupivacaine group) and female reproductive disorders (5 (13.5%) in the Levobupivacaine group and 5(13.9%) in the Bupivacaine group). There was no evidence of any other difference between the two groups.

**Vital signs** – The vital signs including sitting systolic and diastolic blood pressure, maternal heart rate and fetal heart rate were summarized by the study group in NDA Table M1.1 to M1.4 (vol. 116). There was no evidence of difference between the two groups.

**1.4.f. Reviewer's comments and conclusions**

**Efficacy result:** This reviewer agreed with the sponsor's analysis and conclusion in general that it failed to establish dose potency equivalence between Levobupivacaine and Bupivacaine based on the minimum local analgesic concentration (MLAC). The potency of Levobupivacaine to Bupivacaine was estimated to be 0.98. However, based on the 95% confidence interval, one can not rule out a 42% reduction or a 38% increase in potency. Although there was no full analysis carried out for the secondary efficacy endpoints, it was clear that there was no statistical evidence of any difference between the two groups.

**Safety results: Adverse events** – Similar adverse event profile was observed in both treatment groups except adverse events of gastrointestinal system disorders. There was 1 patient (2.7%) with gastrointestinal system disorders in the Levobupivacaine group compared with 6 patients (16.7%) in the Bupivacaine group. The mostly frequent adverse event the patients experienced were fetal disorders (5 (13.5%) in Levobupivacaine group and 5 (13.9%) in Bupivacaine group) and female reproductive disorders (5 (13.5%) in the Levobupivacaine group and 5(13.9%) in the Bupivacaine group). There was no evidence of any other difference between the two groups.

## II. Studies on Central Block

Study #	Design	Dose	Number of treated (safety)	Age mean	Sex(M/F) Race (W,B,O)	Indication
006175	Dbblind / random / parallel	Levobupivacaine -75 mg 0.5%, 112.5mg 0.75% Bupivacaine - 75mg 0.5%	88(88)	47.2 (19-80)	31/75 88, 0, 0	Lower limb surgery / Epidural injection
CS 005	Dbblind / random / parallel	Levobupivacaine -150 mg 0.75% Bupivacaine - 150mg 0.75%	56(56)	52.5 (28-80)	24/32 53, 1, 2	Major abdominal surgery / Epidural injection

### Study Population of Central Block Studies:

#### Inclusion Criteria -

- i. Patients, male or female over the age of 18 years old.
- ii. Patients with American Society of Anesthesiologist (ASA) Class I or II
- iii. Patients undergoing uncomplicated elective limb vascular surgery or arthroscopy appropriate for epidural anesthesia
- iv. Informed written consent

#### Exclusion Criteria – Patients with any of the following conditions

- i. Women who were pregnant or lactating mothers
- ii. Women of child bearing potential not using adequate contraceptive methods
- iii. Patients with a known hypersensitivity to amide local anesthetic
- iv. A known history or presence of severe renal, hepatic, respiratory, or cardiac disease especially those with dysrhythmias or AV block
- v. Patients with neurological, neuromuscular, or psychiatric disorders
- vi. A history of drug or alcohol abuse within the last 6 months
- vii. Blood clotting disorder or blood dyscrasia
- viii. A history of seizure disorder
- ix. Weighed more than 110 kg
- x. Participated in a clinical trial in the last 3 months.

### II.1 Study 006175

II.1.a. Study Objectives: The objectives of the study was to compare the efficacy (duration and onset of anesthesia), plasma concentration and safety profiles of two different concentrations of Levobupivacaine (0.5% and 0.75%) with 0.5% racemic Bupivacaine for dose response evaluation.

II.1.b. Study Design: This was a randomized, double blind, 3 limb parallel group (Levobupivacaine - 15mg of 0.5%, 15 ml of 0.75% and Bupivacaine - 15mg 0.5%) study conducted in three centers in the United Kingdom.

#### II.1.c. Efficacy Endpoints:

Primary measure was the duration of sensory block, which was defined in protocol as