Analysis of Secondary Parameters

"The secondary parameters were to be time to T10 regression, time to complete regression, abdominal wall relaxation (using the RAM score), patient pain rating at each of the three time points, time to onset and offset of motor block, maximum upper level, time to maximum upper level, time to two-level regression, duration of sensory and motor blocks, muscle relaxation assessment, and overall assessment."

"For the computation of the CI, if the time of onset of two-level regression was missing and could not be determined from the dermatome sensory data, then the time of study termination was used."

"The secondary parameters of time to onset or offset were analyzed, using a product-limit (Kaplan-Meier) survival analysis. The ITT population was used in the analysis with treatment as the independent variable. The muscle relaxation (RAM) scores, pain scores, and motor block assessment scores by the patient at each time point, duration of sensory and motor block, maximum upper level, and overall assessment scores were analyzed by a t-test with treatment as the independent variable. If appropriate, a transformation (e.g., arcsine), logistic regression, or non-parametric statistic was to be used."

[Item 8, Vol. 1.66, pp. 035-036]

PROTOCOL AMENDMENT:

Amendments:

On January 30, 1997, Amendment No.1 made the following revisions to the protocol:

- Clarified the procedures for: study drug labeling, study drug storage instructions, study drug accountability, screening, administration of local anesthesia, pharmacokinetic sampling and analysis, efficacy assessments, cardiovascular assessment.

On April 3, 1997, Amendment No.2 made the following revisions to the protocol:

- Added the collection of signal-averaging electrocardiograms (SAECGs) and clarified the procedures for collecting QRS data.

- The follow-up procedures were revised to reflect the study site telephone call between 3 and 7 days post-hospital discharge.

[Item 8, Vol. 1.66, pp. 020-021]

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 57 patients randomized, 56 (98.2%) received study medication – one patient was withdrawn prior to receiving drug due to a violation of the inclusion/exclusion criteria. Patient # 036 randomized to the levobupivacaine group did not meet the height criterion. All 56 patients who received study drug completed the study - 28 in each group. All had post-baseline efficacy and safety data and were considered eligible for the Intent-to-Treat population.

Fifty-five patients who received study drug were considered eligible for the per-protocol population. Patient # 043 in the bupivacaine group did not achieve the protocol – specified sensory block.

Please note sponsor's table below for specifications.

Table 68. Patient Disposition

Table 2 Patient Disposition: Intent-to-Treat Population

Patients	Levobupivacaine N (%)	Bupivacaine N (%)	All Patients N (%)
Randomized	29 (100)	28 (100)	57 (100)
Withdrew Prior to Anesthesia (Did Not Received Study Drug)	1 (3.4)	.0	.1 (1.8)
Received Study Drug (Safety Population)	28 (96.6)	28 (100.0)	56 (98.2)
Received Study Drug (ITT Population)	28 (96.6)	28 (100.0)	56 (98.2)
Per-Protocol Population	28 (96.6)	27 (96.4)	55 (96.5)
Non-Evaluable	0	1 (3.6)	1 (1.8)
Discontinued	1 (3.4)	0	1 (1.8)
Completed	28(96.6)	28 (100.0)	56 (98.2)

Abstracted from Statistical Table 1

[Sponsor's Table 2, "Patient Disposition", Item 8, Vol. 1.66, p. 039]

Patient specific protocol violations are summarized for individual patients in the table below.

Table 69. Patient - Specific Protocol Violations

PROTOCOL VIOLATION	TREATMENT	PATIENT NUMBER
Did Not Achieve Protocol-Specified Sensory Block	Bupivacaine	043
Height Criterion	Levobupivacaine	036

Demographics

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

Table 70. Demographics - All Patients

Table 3 Patient Demographics and Baseline Characteristics: Intent-to-Treat Population

Variable	Levobupivacaine N=28	Bupivacaine N=28	All Patients N=56
Sex N (%)			
Male	12 (42.9)	12 (42.9)	24 (42.9)
Female	16 (57.1)	16 (57.1)	32 (57.1)
Race N (%)			
Caucasian	25 (89.3)	28 (100.0)	53 (94.6)
Black	1 (3.6)	0	1 (1.8)
Asian	0	0	0
Hispanic	0	0	0
Other	2 (7.1)	0	2 (3.6)
Age (years)			
Mean ± S.D.	53.0 ± 13.2	52.0 ± 12.5	52.5 ± 12.7
Median	54.0	53.0	53.0
Minimum	28	28	28
Maximum	80	73	80
Height (cm)			
Mean ± S.D.	169.5 ± 10.2	171.9 ± 8.8	170.7 ± 9.5
Median	170.20	168.90	170.2
Minimum	152.4	157.5	152.4
Maximum	190.5	193.0	193.0
Weight (kg)			
Mean ± S.D.	75.2 ± 14.2	79.7 ± 14.6	77.5 ± 14.5
Median	75.9	77.6	77.3
Minimum	46.3	55.1	46.3
Maximum	101.4	107.6	107.6

Abstracted from Statistical Table 3.2

[Sponsor's Table 3, Item 8, Vol.1.66, p. 040]

atients' ages ranged from 28 to 80 years with a mean age of 52.5 years. A total of 56 patients received drug, of these, 24 (43%) were male and 32 (57%) were female. The majority (97%) of patients were Caucasian.

The physical examination was normal in the majority of cases. In those instances when the exam showed abnormal results, the abnormality was found in the abdomen or genitourinary/anorectal body system in both the levobupivacaine and bupivacaine groups.

Table 71. Physical Examination—Intent-to-Treat Population

Table 4 Physical Examination: Intent-to-Treat Population

	Levobupivacaine			Bupivacaine		
Body System	Normal N (%)	Abnormal N (%)	Not Done N (%)	Normal N (%)	Abnormal N (%)	Not Done N (%)
Head, Neck, Thyroid	25 (89.3)	2 (7.1)	1 (3.6)	27 (96.4)	1 (3.6)	0
Eyes, Ears, Nose, Throat	23 (82.1)	2 (7.1)	3 (10.7)	23 (82.1)	5 (17.9)	0
Chest, including Breasts	18 (64.3)	4 (14.3)	6 (21.4)	23 (82.1)	3 (10.7)	2 (7.1)
Lungs	25 (89.3)	2 (7.1)	1 (3.6)	26 (92.9)	2 (7.1)	0
Heart	28 (100.0)	0	0	26 (92.9)	2 (7.1)	0
Lymph Nodes	19 (67.9)	0	9 (32.1)	20 (71.4)	1 (3.6)	7 (25.0)
Abdomen	16 (57.1)	12 (42.9)	0	16 (57.1)	11 (39.3)	1 (3.6)
Anorectal	14 (50.0)	6 (21.4)	8 (28.6)	12 (42.9)	8 (28.6)	8 (28.6)
Genitourinary	9 (32.1)	15 (53.6)	4 (14.3)	15 (53.6)	7 (25.0)	6 (21.4)
Skin	19 (67.9)	2 (7.1)	7 (25.0)	18 (64.3)	6 (21.4)	4 (14.3)
Musculoskeletal	19 (67.9)	4 (14.3)	5 (17.9)	21 (75.0)	4 (14.3)	3 (10.7)
Neurologic	21 (75.0)	0	7 (25.0)	23 (82.1)	2 (7.1)	3 (10.7)
Other	0	4 (14.3)	0	0	1 (3.6)	0

Abstracted from Statistical Table 4

[Sponsor's Table 4, Item 8, Vol.1.66, p. 041]

Concomitant Medications

The most frequently administered concomitant medication included pre-operative sedative agents, prophylactic agents for nausea, anesthetics , anesthetic reversing agents, vasopressors, and pain medications.

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Measurement:

"The primary measure of efficacy was the time to onset of sensory block (bilateral T10) adequate to carry out surgery. For this key efficacy parameter results are presented for both the ITT population, which is the primary population, and the per-protocol population."

"Patient No.043 (bupivacaine) did not achieve the per-protocol defined adequate block and this patient was excluded from the per-protocol population analysis of time to adequate sensory block. For purposes of ITT analysis, the time to onset of sensory block for this patient was censored at the start time of surgery."

"The results for the two populations are similar. The 90% confidence interval for the mean difference of time to onset of sensory block was - 4.0, 3.2 for the ITT population and -1.4, 3.7 for the per-protocol population. These boundaries are within the ± 7.58 minutes needed to show equivalence; these boundaries were set a priori." Note: the statistical reviewer recalculated the 95% confidence interval and found similar results.

"The log-rank test also shows there was no difference (p> 0.20) between the two treatment groups with respect to the time to onset of adequate sensory block."

[Item 8, Vol.1.66, p. 042 – 043]

Please see sponsor's table below for results of the statistical analysis of the primary endpoint.

APPEARS THIS WAY
ON ORIGINAL

Table 72. Analysis of Primary Efficacy Variable

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

Variable	Levobupivacaine	Bupivacaine	Mean Difference [90% CI]	p-value
N	28	28	-0.4	0.782
Mean ± S.D.	13.6 ± 5.6	14.0 ± 9.9	[-4.0, 3.2]	
Median	15.0	12.5		
Minimum	5	5		
Maximum	30	56		
Adequate Block	N (%)	N (%)		1.000
Yes	28 (100.0)	27 (96.4)		
No	0	1 (3.6)		

Abstracted from Statistical Table 6.1

Table 7 **Time (Minutes) to Onset of Sensory Block: Per Protocol Population**

Variable	Levobupivacaine	Bupivacaine	Mean Difference [90% CI]	p-value
N	28	27	1.2	0.399
Mean ± S.D.	13.6 ± 5.6	12.4 ± 5.6	[-1.4, 3.7]	
Median	15.0	10.0		
Minimum	5	5		
Maximum	30	30		
Adequate Block	N (%)	N (%)		1.000
Yes	28 (100.0)	27 (100.0)		
No	0	0		

Abstracted from Statistical Table 6.2

[Sponsor's Table 6 and 7, Item 8, Vol.1.66, p. 043]

Secondary Efficacy Measurements:

Location and Time to Maximum Upper Level Bilaterally

"No statistically significant differences were found with respect to the location and time to maximum upper level bilaterally. The mean time to maximum upper level (bilaterally) was 24.3 and 26.5 minutes for the levobupivacaine and bupivacaine treatment groups, respectively. The difference between them was 2.2 minutes with a 95% CI of [-8.3, 4.0]. The mean maximum level bilaterally was between T5 andT6 for either group. The difference between the two treatments was 0.3 dermatomes with a 95% CI of [-1.7, 1.2]"

Offset and Duration of Sensory Block

"There were no statistically significant differences between the two groups with respect to the time to T10 regression and time to two-level regression. There was a statistically significant difference between the two groups with respect to the time to complete regression (p=0.016). The mean time to complete regression was 506 minutes for the bupivacaine group and 551 minutes for the levobupivacaine group; a difference between the two groups of 45 minutes (a 95% CI of [2,87])."

Motor Block

"There was a statistically significant difference (p<0.001) between the two groups with respect to proportion of patients experiencing motor block prior to surgery. Four (14%) patients in the levobupivacaine group and 20 (71%) patients in the bupivacaine group experienced motor block (.i.e., score of 2 or 3) prior to surgery."

With respect to the duration of motor block, defined as the offset of motor block from Time 0 (time of injection), three patients (Patient Nos. 019 and 044 in the levobupivacaine group, and Patient No. 037 in the bupivacaine group) who did not achieve motor block (i.e., score of 0) during treatment were excluded from the analysis. No statistically significant difference was found (p=0.311). The mean difference in duration of motor block was approximately 20 minutes (355.4 – levobupivacaine and 375.7 – bupivacaine) with a 95% CI of -71 minutes to 30 minutes.

The sponsor has not analyzed the time to onset of motor block as specified in the protocol, but has analyzed the time to onset of pre-surgery Grade 3 motor block. The statistical ramifications of this will be discussed in the statistical review.

Abdominal Muscle Relaxation

"The pre-surgery RAM score at 30 minutes was lower with levobupivacaine (mean = 3.4) compared to bupivacaine (mean = 3.8). The mean difference was 0.4 points and the 95% CI was within one RAM rating point [-0.9,0.0). There were no statistically significant differences between the two groups with respect to other pre-surgery RAM scores."

[Item 8, Vol. 1.66, pp. 043 - 047]

Overall Assessments

The anesthesiologist and surgeon provided an overall assessment of muscle relaxation. The surgeon rated muscle relaxation scores were higher in the levobupivacaine treatment group (mean of 2.3) compared to the bupivacaine treatment group (mean of 2.0). The difference tended toward, but did not achieve, statistical significance (p = 0.074) No other statistically significant differences between the two groups were found."

The anesthesiologist assessment of muscle relaxation was also not statistically significant (p=0.505). The mean value given for levobupivacaine was 2.3 vs 2.2 for bupivacaine. The mean difference was 0.1 [95%CI:-0.3,0.6].

No analysis of the overall assessment of block was performed as specified in the protocol.

Patient Assessment of Pain

Patients assessed their level of pain on a scale of 0 = none to 3 = severe during surgery, at the conclusion of surgery, and prior to leaving recovery room. No statistically significant differences were found at any of these time points. Patients in the levobupivacaine group had less pain (mean of 0.2) at the conclusion of surgery (p=0.072) compared to patients in the bupivacaine group (mean of 0.6). The mean difference was 0.4 points and the 95% CI was within one rating point [-0.8, 0.01).

[Item 8, Vol. 1.66, pp. 043 - 047]

Table 73. Analysis of Secondary Efficacy Variables

Table 8 **Time[1] (Minutes) to Maximum Upper Level (Bilateral): Intent-to-Treat Population**

Variable	Levobupivacaine	Bupivacaine	Mean Difference [95% CI]	p-value
N	28	28	-2.2	0.642
Mean ± S.D.	24.3 ± 9.4	26.5 ± 13.2	[-8.3, 4.0]	
Median	25.0	20.0		
Minimum	10	15		
Maximum	60	60		

Relative to time of 5 mL dose administration.

Abstracted from Statistical Table 7

Table 9 **Maximum Upper Level (Bilateral): Intent-to-Treat Population**

Variable	0.75% Levobupivacaine	0.75% Bupivacaine	Mean Difference [95% CI]	p-value
N	28	27	-0.3	0.729
Mean ± S.D.	13.3 ± 2.1	13.5 ± 3.1	[-1.7, 1.2]	
Median	13.0	13.0		
Minimum	10	7		
Maximum	18	21		

Abstracted from Statistical Table 7

[Sponsor's Table 8 and 9, Item 8, Vol. 1.66, pp. 044]

Table 74. Analysis of Secondary Efficacy Variable

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

Variable	Levobupivacaine	Bupivacaine	Mean Difference [95% CI]	p-value
T10 Regression				
N	28	27	35.0	0.216
Mean ± S.D.	375.0 ± 87.8	340.1 ± 95.5	[-14.6, 84.6]	
Median	345.0	360.0		
Minimum	210	150		
Maximum	571	480		
Complete Regression				
N	28	28	44.6	0.016
Mean ± S.D.	550.6 ± 87.6	505.9 ± 71.1	[1.9, 87.4]	
Median	555.0	510.0		
Minimum	390	360		
Maximum	780	630		
Two Level Bilateral Regression				
N	28	28	8.1	0.917
Mean ± S.D.	300.8 ± 81.4	292.7 ± 99.6	[-40.6, 56.9]	
Median	278.0	255.0		
Minimum	210	120		
Maximum	510	514		

Abstracted from Statistical Table 13

Table 75. Analysis of Secondary Variable

Table 11 Duration of Sensory Block: Intent-to-Treat Population

Variable	Levobupivacaine	Bupivacaine	Mean Difference [95% CI]	p-value
N	28	27	33.8	0.183
Mean ± S.D.	361.6 ± 89.7	327.7 ± 96.2	[-16.5, 84.1]	
Median	332.5	345.0		
Minimum	180	135		
Maximum	561	470		

Abstracted from Statistical Table 15

[Sponsor's Table 10 and 11, Item 8, Vol. 1.66, pp. 045]

Table 76. Analysis of Secondary Efficacy Variable

Table 12 Duration of Motor Block: Intent-to-Treat Population

Variable	Levobupivacaine	Bupivacaine	Mean Difference [95% CI]	p-value
N	26	27	-20.3	0.311
Mean ± S.D.	355.4 ± 83.4	375.7 ± 99.2	[-70.9, 30.4]	
Median	345.0	360.0		
Minimum	240	210		
Maximum	510	600		

Abstracted from Statistical Table 14

Table 77. Analysis of Secondary Efficacy Variable

Table 13 Overall Assessment of Muscle Relaxation: Intent-to-Treat Population

Variable	Levobupivacaine	Bupivacaine N (%)	Mean Difference [95% CI]	p-value
Anesthesiologist				
N	8	28	0.1	0.505
Mean ± S.D.	2.3 ± 0.67	2.2 ± 0.90.	[-0.3, 0.6]	
	N (%)	N (%)		
0=poor	0	1/28 (3.6)		
1=fair	3/28 (10.7)	6/28 (21.4)		
2- good	13/28 (46.4)	8/28 (28.6)		
3=excellent	12/28 (42.9)	13/28 (46.4)		
Surgeon				
N	28	28	0.4	0.074
Mean ± S.D.	2.3 ± 0.67	2.0 ± 0.79	[-0.0, 0.8]	
	N (%)	N (%)		
0=poor	0	1/28 (3.6)		
1=fair	3/28 (10.7)	6/28 (21.4)		
2- good	13/28 (46.4)	14/28 (50.0)		
3=excellent	12/28 (42.9)	7/28 (25.0)		

Abstracted from Statistical Table 11

[Sponsors Table 12 and 13, Item 8, Vol. 1.66, pp. 046 and 047]

REVIEWER'S EFFICACY DISCUSSION

The primary efficacy variable was time to onset of sensory block. The 0.75% levobupivacaine group achieved sensory block in a mean time of 13.6 minutes as compared to 14.0 minutes for the 0.75% bupivacaine group. ($p = 0.782$).

There was a statistically significant difference in the time to complete regression of sensory block ($p = 0.016$), however, i.e., 506 minutes for the bupivacaine and 551 minutes for levobupivacaine, a difference of 45 minutes. Clinically, a 45 minute difference between levobupivacaine and bupivacaine with respect to time to complete regression of block is of specific relevance.

Overall, the clinical data proves that the product, 0.75% levobupivacaine, is effective as an epidural anesthetic when administered to patients undergoing major abdominal surgery, despite the lack of statistically significance. This conclusion is based upon the clear evidence that patients experienced some level of analgesia sufficient for major abdominal surgery

STUDY # 030475

PROTOCOL SYNOPSIS:

Title: "A Study to Assess the Efficacy and Safety of Three Concentrations of Levobupivacaine Administered as a Continuous Infusion for Post-Operative Pain in Patients Undergoing Elective Orthopedic Surgery."

Primary Objective: To compare the analgesic efficacy of three different concentrations of levobupivacaine.

Secondary Objective: To determine the safety profile of the three concentrations of Levobupivacaine.

[Item 8, Vol. 1.68, p. 021]

Study Design:

. ne study is designed as a randomized, multi-center, double blind, 3-limb parallel group, study of the efficacy, of 3 doses of levobupivacaine (0.0625%, 0.125% and 0.25%) administered as a continuous infusion at 6 ml/hr. The study population consisted of patients who required elective orthopedic surgery. They were randomized in equal proportions to the 3 treatment groups and stratified by the joint to be replaced, i.e., knee or hip. There were a total of 91 evaluable patients.

Group I	0.625% levobupivacaine
Group II	0.125% levobupivacaine
Group III	0.25% levobupivacaine

Eligible patients were male or female, ASA Class I or III between 18 and 80 years of age, consenting to receive epidural anesthesia for elective orthopedic surgery. Patients were not pregnant or lactating, were using an adequate contraceptive method, had no systemic illness, had no history of alcohol or opioid abuse in the preceding 6 months, or participated in no clinical trials in the previous month. In addition, patients who would undergo controlled passive movement therapy during the study were excluded.

Patients were given 20 mg of temazepam and 150 mg of ranitidine pre-operatively, as well as non-steroidal anti-inflammatory drugs the night before surgery, if required. All patients received i.v. antibiotics for prophylaxis according to hospital protocol.

Initially, a 3ml test dose of study drug was given, if after 5 minutes, there was no evidence of intravascular or subarachnoid injection, the remaining 7ml of study drug was given. Following placement of the epidural catheter and injection of the 10 ml of study drug, (time 0 minutes) further 5-ml injections were given as needed to achieve an adequate sensory level for surgery. Thirty minutes after the last bolus epidural injection, an infusion of ?.0625%, 0.125% or 0.25% levobupivacaine was administered (Time 0) at a rate of 6 ml/hr for a period of 24 ›urs.

The primary measure of efficacy was the time to the first request for analgesia during the 24-hour infusion period. At the initial request for post-operative rescue analgesia, patients received 2 mg of i.v. morphine until an acceptable level of analgesia was obtained. Thereafter, the PCA pump was activated and patients were allowed to titrate the morphine themselves.

Sensory block was also measured (1) immediately before the initial administration of morphine, (2) 10 and 20 min after the last administration of the morphine. (3) hourly until 4 hours following the start of the epidural infusion of study drug, provided surgery was over, (4) 2 hourly for the next 8 hours and (5) 6 hourly thereafter up to 24 hour if patients were awake.

APPEARS THIS WAY
ON ORIGINAL

response to FDA posed questions to the sponsor regarding the total amount of patient-administered morphine, e sponsor has provided the following table:

Table 78. Total Morphine Administered per Treatment Group[4]

Total Morphine in mg (Total Bolus & PCA)			
	0.0625 % Levobupivacaine	0.125 % Levobupivacaine	0.25 % Levobupivacaine
N	31	27	32
Mean	35.58	29.44	13.28
SD	24.26	22.40	16.63
Min	7	0	0
Max	106	99	57

Motor block was assessed on the 'non-operated' limb using the modified Bromage scale (1) hourly until 4 hours following the start of the epidural infusion, (provided surgery was over), (2) 2 hourly for the next 8 hours and (3) 6 hourly thereafter up to 24 hour, if patients were awake.

Patients recorded their pain hourly until 4 hours following the start of the epidural infusion, (provided surgery was over), 2 hourly for the next 8 hours and 6 hourly thereafter up to 24 hour if patients were awake using the Visual Analog Scale (VAS). In addition, the VAS scores were assessed immediately before the initial administration of the 2-mg morphine dose. Level of sensory block was assessed 15 min after the second bolus injection. If at this time the patient still does not have an adequate level of sensory block, the patient was withdrawn.

.and held visual analog scale rulers were used to assess pain scores, where '0 = no pain' and '100 = worst imaginable pain'.

The modified Bromage scale is as follows:

0 = no paralysis, full flexion of the knee and ankle
1 = inability to raise extended leg, able to move knee
2 = inability to flex knee, able to flex ankle
3 = inability to move lower limb

[4] Parexel Int'l Corp. – fax received 12/21/98.

Table 79. Schedule of Assessments – (Sponsor's Table Item 8, Vol. 1.68, p. 024)

TABLE I

Schedule of Assessments

Assessment	Timepoint																		
	Pre-Study	Pre-Operative Extradural Injection	15 min	30 min	Extradural Infusion	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	18 h	24 h	Post Surgery	Post Extradural Infusion	At Discharge#	Follow-up (3-7 days Post-discharge)#
Written consent	X																		
Screening assessments	X																		
Medical history and physical examination	X																		
Visual analogue scale**						X	X	X	X	X	X	X	X	X	X				
Assessment of sensory block*			X	X		X	X	X	X	X	X	X	X	X	X				
Assessment of motor block						X	X	X	X	X	X	X	X	X	X				
Laboratory analyses	X																X		
Vital signs	X									X			X	X	X				
12-lead ECG	X																		
Adverse events																X	X	X	X
Concomitant medications	X															X	X	X	X

* = The 30 min assessment will be performed if block adequate for surgery is not achieved after 15 min. In addition, sensory block will be assessed before the first 2 mg injection of morphine is given as rescue analgesia and 10 and 20 min after the last 2 mg injection of morphine has been given.

** = In addition, VAS score will be obtained immediately before the first dose of morphine is given as rescue analgesia.

= The follow-up period changed according to Amendment 2 to be all medications used and any adverse events experienced in the 12 h following removal of the extradural infusion and at 3-7 days post-surgery, concomitant medication and adverse events determined to be related to the study medication.

Safety Monitoring

Heart rate, systolic and diastolic arterial pressure, sensory and motor block will be monitored during surgery and a 5-lead ECG will be performed at an appropriate time during surgery.

STATISTICAL ANALYSIS

"The analysis of efficacy data was performed on 'intent-to-treat' and 'per-protocol' populations. The 'intent-to-treat' population was defined as all randomised patients excluding patients that did not receive any of the randomised study drug and patients who, during the administration procedure, suffered an intravenous or subarachnoid injection resulting in immediate withdrawal from the study."

"All patients, except those who did not receive the randomised study drug, were included in the evaluation of safety data."

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

"The primary measure of efficacy was defined as the time to first request for analgesia during the 24 h following the start of the extradural infusion using the 'intent-to-treat' population."

"This response has been analysed using analysis of variance (ANOVA) with terms for treatment centre, joint *(ie* knee or hip) and treatment by centre interaction. An additional supportive analysis has been performed to include additional terms for treatment by joint, centre by joint and treatment by centre by joint interactions. Any interaction term not significant at the 10% level was dropped from the model and the analysis was repeated. Using the error variance from the ANOVA, pairwise comparisons of the 3 treatment means were made using Student's 't'-tests. To compensate for multiple comparisons, a sequentially rejective Bonferroni-Holm method was used *(ie* in order to attain an overall 5% significance level, the greatest difference between treatments was the significance level 1.7%, the second greatest difference was the *2.5%* level and the smallest difference was the *5%* level). Estimates of treatment differences and the associated *95%* confidence interval have been presented together with the p-value for the 't'-tests and the significance level for the 't'-tests using a sequentially rejective Bonferroni-Holm method."

"The residuals from this analysis were submitted to a Shapiro-Wilk test for normality and examined graphically to assess variance homogenicity."

[Item 8, Vol. 1.68, pp. 041-043]

The primary efficacy variable included censored observations *(ie* patients not requesting the analgesia during the 24 h period) thus a secondary analysis using survival techniques was done. The proportion of patients requesting relief analgesia was illustrated using Kaplan-Meier survival curves. In addition, a Cox's proportional hazard regression model was fitted including terms for treatment, centre, joint *(ie* knee or hip) and treatment by centre interaction. However, it was found that the assumption of proportionality between all 3 survival rates was not satisfied, so separate pairwise comparisons were carried out. To compare the 0.0625% and the 0.25% levobupivacaine treatment groups and the 0.125% levobupivacaine treatment groups, a Cox's proportional hazard regression model including terms for treatment, centre, joint and treatment by centre was fitted to each pair (the proportionality assumption was satisfied for each pair of treatment groups)."

"To compare the 0.0625% and the 0.125% levobupivacaine treatment groups, it was decided that a Wilcoxon 2 sample test using centre and surgery type as prognostic factors would be appropriate. Unfortunately, the 2 factors could not be used together as they produced too many strata with not enough data in each. Therefore the centre and surgery type were considered separately, 50 2 test statistics were produced (an assumption of a non-significant centre by surgery type interaction was made)."

"To compensate for multiple comparisons, a sequentially rejective Bonferroni-Holm method was used *(ie* in order to attain 5% significance level, the greatest difference between treatments was required to attain significance at 1.7%, the second greatest difference at the 2.5% and the smallest difference at the 5% level)."

"In addition, the median, 25 th, 75 th, and 90 th percentiles for the time to first relief analgesia together with the interquartile range have been tabulated (both including and excluding censored observations)."

[Item 8, Vol. 1.68, pp. 043-044]

Secondary Efficacy Variable

Normalized Dose of Morphine Administered

"The normalised dose of morphine administered during the time of the extradural infusion was taken to be the sum of the total dose of morphine administered by bolus injection and during the extradural infusion *via* the PCA pump divided by the time of the extradural infusion. If the time of the extradural infusion was greater than 25 h, the patients were not included in the analysis. In addition, the normalised number of requests for analgesia made during the extradural infusion was analysed. Again, patients with extradural infusion for longer than 25 h were not included in the analysis."

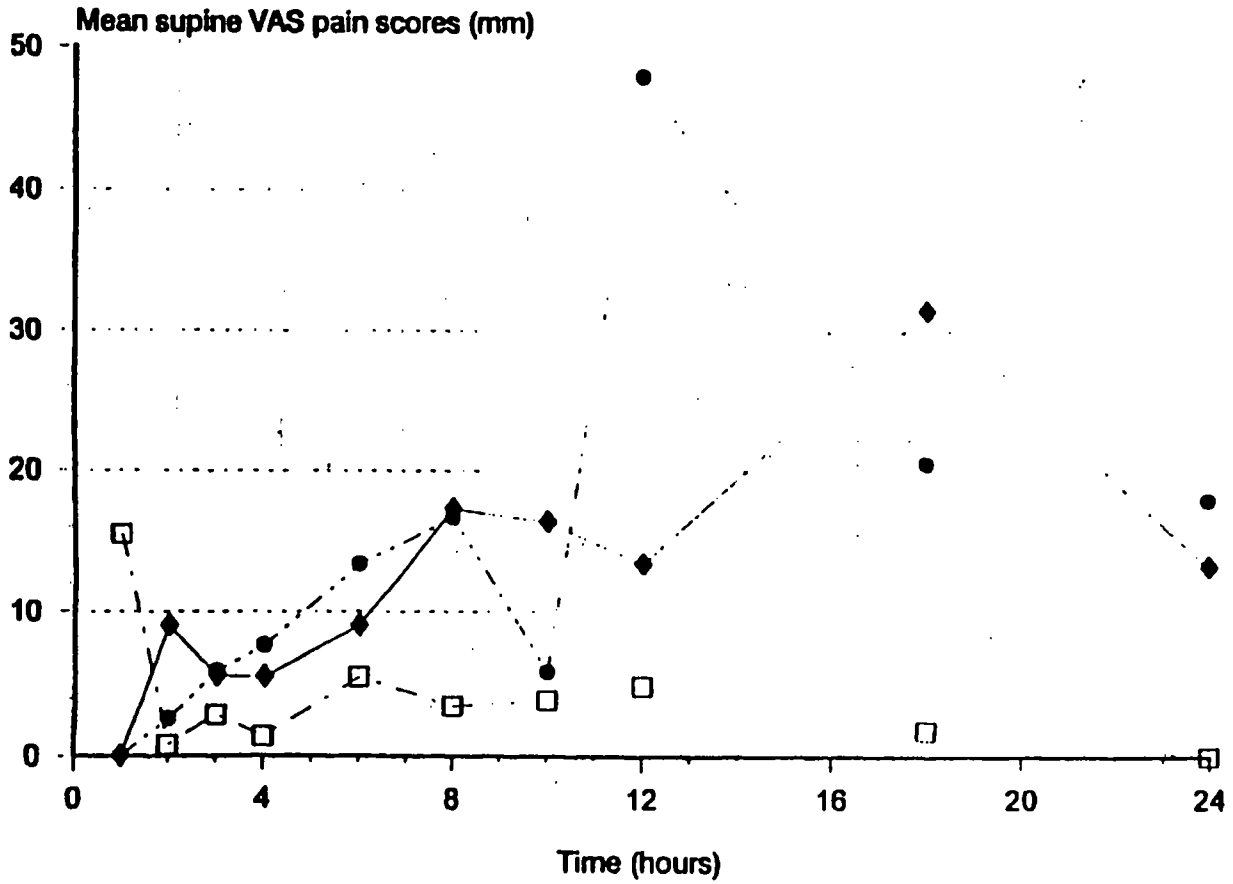
"These endpoints were both initially analysed in the same way as the primary measure *(ie* ANOVA). However, the residuals from both models deviated from the assumptions of an ANOVA, so re-analyses of the data sets were required. Since zero values were present *(ie* patients who did require any rescue analgesia during the extradural infusion period), a log transformation of the data was considered inappropriate, so non-parametric methods were used, namely the Wilcoxon two-sample test. To compensate for multiple comparisons, a sequentially rejective Bonferroni-Holm method was used *(ie* in order to attain 5% significance level, the greatest difference between treatments was required to attain significance at 1.7%, the second greatest difference at the 2.5% and the smallest difference at the 5% level). The estimate of treatment difference and associated 95% confidence intervals for both sets of data were based on Wilcoxon's two-sample test."

Visual Analogue Pain Scores

"The visual analogue pain scores (VAS) were recorded hourly until 4 h post-extradural injection completion rovided surgery was over), 2 hourly for the next 8 h and 6 hourly thereafter up to 24 h provided the patient was awake. A 10 cm visual analogue scale was used from 0-10 where '0 = no pain' and '10 = worst imaginable pain'" The sponsor offered a graphical illustration as representative of the study results (see Figure 1.0 below).

[Item 8, Vol. 1.68, pp. 044-045]

LEVOBUPIVACAINE - 030475
FIGURE 3.2
Mean VAS scores (mm) prior to analgesia against time (h)
by treatment group
Intent-to-treat population



Height of Sensory Block

In order to summarise the height of sensory block, scores were assigned to the upper and lower dermatomes as follows: scores 1, 2, 3,..., 8 to dermatomes C1, c2, C3, ..., C8, 9, 10,..., 20 to dermatomes Th1 to Th12 (sometimes written as T1 to T12), 21, 22,..., 25 to L1 to L5 and 26, 27, 30 to S1 to S5 respectively. From this, the median score, 25 th and 75 th percentiles for each treatment group at each timepoint were calculated. Once the median and percentiles were calculated they were formatted back to the dermatome name."

Motor Block

"Analysis of the maximum grade of motor block achieved has been performed using a logit model with terms for treatment, centre, joint *(ie* knee or hip). Pairwise comparisons between treatment groups were carried out using the Wald test statistic with the sequentially rejective Bonferroni-Holm method also applied. The odds ratio estimate of treatment difference and associated 95% confidence interval have been presented. The score test for goodness-of-fit was used in order to test the proportional odds assumption."

"All statistical analyses have been performed using two-sided tests and a 5% significance level throughout. In general terms, data from those patients that were withdrawn and/or data that were missing, have been included in such a way as to minimise bias."

[Item 8, Vol. 1.68, pp. 046-047]

PROTOCOL AMENDMENT:

Amendment 1 dated 1/21/97, Amendment 2 dated 5/9/97 and Amendment 3 dated 6/11/97 and Amendment 4 (never effective) dated 8/19/97 made the following changes:

A. Study Procedures

- The sponsor has deleted the 2 minute rhythm strip from the pre-operative evaluations – reason not specified.
- The description of Time 0 has been changed from, "... the end of the epidural injection", to, "... the start of the epidural infusion. This change has been reiterated throughout the document where appropriate.
- The length of epidural space allowed for injection of study drug has been increased from T12/L1 to L2/L3
- The criteria for withdrawal will include those patients whose surgery lasts longer than 4 hours.
- The length of the sensory block assessments has been extended an additional 15 minutes
- The sponsor has clarified the starting time of the epidural infusion to be after the last bolus injection.

B. Post-operative Period

- The sponsor has chosen to substitute the phrase "... the end of the epidural injection", for, "... the start of the epidural infusion.

C. Primary Measure of Efficacy

- The sponsor has chosen to substitute the phrase "... the end of the epidural injection", for, "... the start of the epidural infusion.

Amendment four was never effective - it did not obtain Ethics Committee approval at any center before the last patients were recruited.

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 105 patients randomized, 36 (34.3%) were randomized to receive 0.0625% levobupivacaine, 33 (31.4%) to receive 0.125% levobupivacaine, and 36 (34.3%) to receive 0.25% levobupivacaine. Three patients (#'s 137, 138, and 152) were randomized but were not included in any population for analysis – their details arrived after the database was locked.

Of the 105 patients randomized, 7 (6.6%) patients were excluded from the safety population, 7 (6.6%) patients were excluded from the Intent-to-Treat population, and 15 (14%) were excluded from the per-protocol population. The most common reason for withdrawal was insufficient block.

Table 80. Patient Disposition

Patients	0.0625% L-bupivacaine N (%)	0.125% L-bupivacaine N (%)	0.25% L-bupivacaine N (%)	Total N (%)
Randomized	36 (34.3%)	33 (31.4%)	36 (34.3%)	105
Excluded from Safety Population	2	4	1	7
Safety Evaluable	34 (94.4%)	29 (87.8%)	35 (97.2 %)	98 (93.3 %)
Excluded from ITT Population	2	2	3	7
Intent-to-Treat Population	32 (94.1%)	27 (93.1%)	32 (91.4%)	91 (86.7%)
Excluded from Per-Protocol	4	6	5	15
Per-Protocol Population	28 (87.5%)	21 (78%)	27 (84.3 %)	76 (72.3 %)

Table 81. Patient Specific Protocol Violations

PROTOCOL VIOLATION	TREATMENT	PATIENT NUMBER	CENTER
Excluded from Safety Population:			
Surgery Postponed	0.0625% Levobupivacaine	64	3
Technical Failure	0.0625% Levobupivacaine 0.125% Levobupivacaine	156 47,178	2 2,3
Insufficient Ward Staffing	0.125% Levobupivacaine	42	2
Anesthesiology Staff Unavailable	0.125% Levobupivacaine	145	2
Surgeon Unavailable	0.25% Levobupivacaine	87	3
Excluded from Intent-to-Treat Population:			
Insufficient Block	0.0625% Levobupivacaine 0.25% Levobupivacaine	132,72 41,66,73	2,3 2,3,3
Adverse Event [5]	0.125% Levobupivacaine	40	1
Consent Withdrawn	0.125% Levobupivacaine	181	3
Excluded from Per-Protocol Population:			
Received Prohibited Medications [6]	0.0625% Levobupivacaine 0.125% Levobupivacaine 0.25% Levobupivacaine	103 134,165 3,102,189	1 2,3 1,1,3
Time Window Violation [7]	0.0625% Levobupivacaine 0.125% Levobupivacaine 0.125% Levobupivacaine 0.25% Levobupivacaine	32 69,180 1 71,175,187 166,169	2 3 1 3 3

[5] Adverse event - sever bradycardia (<30/min) with transient severe decreased cardiac output

[6] Patients who received NSAIDS or other analgesics between 22:00 on the day before surgery and the end of the 24 hour infusion

[7] Patients who had time window violations (between the epidural injection and the epidural infusion)

Demographics

ne following table summarizes the demographic characteristics of the three treatment groups:

Table 82. Demographics - Intent-to-Treat Population

TABLE 7

LEVOBUPIVACAINE - 030475

Demographic details

by treatment group

Intent-to-treat population

Variable		Levobupivacaine 0.0625% (n=32)		Levobupivacaine 0.125% (n=27)		Levobupivacaine 0.25% (n=32)	
Sex	male	15	(46.9%)	14	(51.9%)	17	(53.1%)
	female	17	(53.1%)	13	(48.1%)	15	(46.9%)
Age (years)	mean	62.3		63.5		65.7	
	sd	12.3		11.3		8.6	
	minimum	32		34		39	
	maximum	80		79		76	
	n	32		27		32	
Race	white	30	(93.8%)	26	(96.3%)	32	(100.0%)
	black	0	(0.0%)	0	(0.0%)	0	(0.0%)
	hispanic	0	(0.0%)	0	(0.0%)	0	(0.0%)
	asian	2	(6.3%)	1	(3.7%)	0	(0.0%)
	other	0	(0.0%)	0	(0.0%)	0	(0.0%)
Height (cm)	mean	164.2		164.2		167.7	
	sd	9.9		10.3		7.9	
	minimum	148		148		151	
	maximum	181		196		183	
	n	31		26		32	
	missing	1		1		0	
Weight (kg)	mean	78.71		74.48		77.36	
	sd	15.30		12.66		11.18	
	minimum	48.0		44.0		54.4	
	maximum	108.5		96.4		102.4	
	n	32		27		32	

[Sponsor's Table 7, Item 8, Vol.1.68, p. 091]

The majority of patients in this study were Caucasian, i.e., 102 (97.1%). Two patients in the 0.0625% levobupivacaine group and one patient in the 0.125% Levobupivacaine group were Asian. In the Intent-to-Treat group, there was 1:1 ratio of males to females. This was also true for the 0.0625% Levobupivacaine and 0.125% Levobupivacaine per-protocol treatment groups. The 0.25% Levobupivacaine per-protocol treatment group consisted of 17 males and 10 females.

A mean age of approximately 65 was found in all three treatment groups. The majority of patients underwent hip surgery (62 patients) versus 43 patients who underwent knee surgery.

All patients in the Intent-to-Treat population reported ongoing significant medical histories involving most commonly the musculoskeletal, circulatory, digestive and respiratory systems. Patients in the 0.0625% levobupivacaine group reported 134 significant medical histories in total, 102 in the 0.125% levobupivacaine group and 128 in the 0.25% levobupivacaine group.

The physical examination showed similar results in all three treatment groups. The only body system which showed some difference between groups was 'heart' with 4 patients (12.5%) in the 0.0625% Levobupivacaine treatment group, 4 patients (14.8%) in the 0.125% levobupivacaine treatment group and 9 patients (28.1%) in the 0.25% levobupivacaine treatment group.

All patients in the Intent-to-Treat population reported taking at least one concomitant medication at screening which was stopped before dosing. Patients in the 0.0625% Levobupivacaine group reported a total of 150 therapies, 120 in the 0.125% levobupivacaine treatment group and 154 in the 0.25% levobupivacaine treatment group.

There were 17 patients (53.1%) in the 0.0625% levobupivacaine treatment group who reported 50 continuing concomitant therapies, i.e., continuing after dosing, 16 patients (59.3%) in the 0.125% levobupivacaine group who reported 37 therapies and 18 patients (56.3%) in the 0.25% levobupivacaine group who reported 40 therapies. In the Intent-to-Treat population, these medications were in the general anti-infectives, central nervous system and blood and blood forming organs categories.

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

Table 83. Medical History

TABLE IV

Medical History Details (excluding surgical histories)

ICD-Body System Procedures in Medicine	Treatment					
	Levobupivacaine 0.0625%		Levobupivacaine 0.125%		Levobupivacaine 0.25%	
	N	%	N	%	N	%
Infections and parasitic disease	1	3.1	0	0	1	3.1
Neoplasms	1	3.1	0	0	0	0
Endocrine, nutritional, metabolic, immunity	5	15.6	3	11.1	5	15.6
Blood and blood-forming organs	2	6.3	0	0	2	6.3
Mental disorders	0	0	0	0	1	3.1
Nervous system and sense organs	1	3.1	2	7.4	3	9.4
Circulatory system	10	31.3	15	55.6	14	43.8
Respiratory system	8	25	4	14.8	5	15.6
Digestive system	10	31.3	10	37	7	21.9
Genitourinary system	3	9.4	2	7.4	5	15.6
Skin and subcutaneous tissue	1	3.1	0	0	3	9.4
Musculoskeletal + connective tissue	32	100	27	100	32	100
Congenital abnormalities	1	3.1	0	0	1	3.1
Symptoms, signs and ill-defined conditions	6	18.8	2	7.4	5	15.6
Injury and poisoning	0	0	1	3.7	1	3.1
Other procedures for diagnosis	1	3.1	0	0	0	0
History of allergy	5	15.6	3	11.1	5	15.6
Contrast radiography	1	3.1	0	0	0	0
Problems with senses and other functions	0	0	1	3.7	0	0

[Sponsor's Table IV, "Medical History..", Item 8, Vol. 1.68, p. 055]

Table 84. Concomitant Medications

TABLE V

Concomitant Medication Reported at Screening but Stopped Prior to Dosing

ICD-Body System Procedures in Medicine	Treatment					
	Levobupivacaine 0.0625%		Levobupivacaine 0.125%		Levobupivacaine 0.25%	
	N	%	N	%	N	%
Alimentary tract and metabolism	30	93.8	27	100	29	90.6
Anti-parasitic products	1	3.1	0	0	0	0
Blood and blood forming organs	2	6.3	0	0	0	0
Cardiovascular system	2	6.3	0	0	2	6.3
Central nervous system	32	100	27	100	32	100
General antiinfectives for systemic use	1	3.1	0	0	2	6.3
Genito urinary system and sex hormones	0	0	0	0	2	6.3
Musculo-skeletal system	14	43.8	10	37	19	59.4
Respiratory system	2	6.3	0	0	0	0
Sensory organs	2	6.3	0	0	4	12.5
Various	1	3.1	1	3.7	0	0

Table 85. Continuing Medications

TABLE VI

Concomitant Medication Reported at Screening and Continuing after Dosing

ICD-Body System Procedures in Medicine	Treatment					
	Levobupivacaine 0.0625%		Levobupivacaine 0.125%		Levobupivacaine 0.25%	
	N	%	N	%	N	%
Alimentary tract and metabolism	10	31.3	6	22.2	6	18.8
Anti-parasitic products	1	3.1	0	0	1	3.1
Blood and blood forming organs	1	3.1	2	7.4	1	3.1
Cardiovascular system	12	37.5	11	40.7	8	25
Central nervous system	3	9.4	2	7.4	3	9.4
Dermatologicals	0	0	0	0	1	3.1
Genito-urinary system and sex hormones	2	6.3	2	7.4	0	0
Musculo-skeletal system	1	3.1	2	7.4	2	6.3
Respiratory system	4	12.5	2	7.4	2	6.3
Sensory organs	0	0	1	3.7	0	0
Systemic hormonal preparations (excluding sex hormones)	2	6.3	1	3.7	3	9.4

[Sponsor's Table V, and VI, Item 8, Vol. 1.68, p. 058 - 059]

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Measurement:

Time to First Request for Rescue Analgesia

"The mean time to the first request for analgesia was highest in the 0.25% levobupivacaine treatment group at 16.664 h compared with 8.106 h in the 0.0625% levobupivacaine treatment group and 9.506 h in the 0.125% levobupivacaine treatment group. In the Intent-to-Treat population, the number of patients who did not require any relief in the 0.25% levobupivacaine treatment group was 15 patients (46.9%), compared with 3 patients (11.1%) in the 0.125% levobupivacaine treatment group and 1 patient (3.1%) in the 0.0625% levobupivacaine treatment group."

"Following a Bonferroni-Holm adjustment, the pairwise comparisons detected, on average, a significantly longer time to first request in the 0.25% levobupivacaine groups compared with both 0.125% and 0.0625% levobupivacaine ($p<0.001$ in both cases). The mean estimate of treatment difference between the 0.125% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group (0.125% levobupivacaine - 0.25% levobupivacaine) was -6.888 h with a 95% confidence interval of -10.521 to -3.255 h. This means that, on average, the time to first request for analgesia was 6.888 h longer in the 0.25% levobupivacaine group compared with the 0.125% levobupivacaine group. The mean estimate of the treatment difference between the 0.0625% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group (0.0625% levobupivacaine - 0.25% levobupivacaine) was -8.120 h with a 95% confidence interval for the difference of -11.587 to -4.652 h. This means that, on average, the time to first request for analgesia was 8.120 h longer in the 0.25% levobupivacaine group compared with the 0.0625% levobupivacaine group."

"There was no statistically significant difference between the 0.0625% levobupivacaine treatment group and the 0.125% levobupivacaine treatment group with respect to time to first request for analgesia ($p=0.49$). However, the estimate of the difference between the treatments (0.0625% levobupivacaine - 0.125% levobupivacaine) was -1.231 h, and the 95% confidence interval was 4.828 to 2.365 h."

"The Kaplan-Meier curves fitted for the secondary analysis show that the 0.25% levobupivacaine treatment group had a higher survival rate than the other 2 treatments for any time greater than 2 h after the start of the extradural infusion."

[Item 8, Vol. 1.68, p. 059 - 061]

he secondary analysis pairwise comparisons for the 0.125% levobupivacaine treatment group *vs* the 0.25% levobupivacaine treatment group and the 0.0625% levobupivacaine treatment group *vs* the 0.25% levobupivacaine treatment group were performed using Cox's proportional hazard models. For both models fitted, the treatment terms were significant ($p<0.001$) after adjustment using the Bonferroni-Holm method. The hazard ratio estimate for 0.125% levobupivacaine *vs* 0.25% levobupivacaine was 1.791, with 95% confidence interval of 1.296 to 2.475 ie the risk of requesting morphine was 1.791 times higher in the 0.125% levobupivacaine compared with 0.25% levobupivacaine. The hazard ratio estimate for 0.0625% levobupivacaine *vs* 0.25% levobupivacaine was 4.181, with 95% confidence interval of (2.210 to 7.907 ie the risk of requesting morphine was 4.181 times higher in the 0.0625% levobupivacaine compared with 0.25% levobupivacaine. These results confirm the results of the primary analysis, namely that time to first request was significantly longer in the 0.25% levobupivacaine group compared with the 0.125% and 0.0625% groups."

"As expected, from the similarity between the Kaplan-Meier curves for the 0.0625% levobupivacaine treatment group and the 0.125% levobupivacaine treatment group, the 2 test statistics produced from the Wilcoxon tests demonstrated no significant difference (centre: $p=0.19$, surgery type: $p=0.80$)."

"For the per-protocol population, similar results were produced for the treatment groups. It was noted that the mean time to first request for analgesia for the 0.25% levobupivacaine treatment group had decreased to 15.852 h. However this value was still considerably higher than those of the other 2 treatments."

"Following a Bonferroni-Holm adjustment, the pairwise comparisons detected significantly longer time to first request in the 0.25% levobupivacaine groups compared with both 0.125% and 0.0625% levobupivacaine ($p<0.001$ in both cases). The mean estimate of treatment difference between the 0.125% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group hours (0.125% levobupivacaine - 0.25% levobupivacaine) was -6.927 h with a 95% confidence interval of -10.823 to -3.030 h. This means that, on average, time to first request for analgesia was 6.927 h longer in the 0.25% levobupivacaine group compared with the 0.125% levobupivacaine group. The mean estimate of the treatment difference between the 0.0625% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group (0.0625% levobupivacaine - 0.25% levobupivacaine) was -7.934 h with a 95% confidence interval for the difference of- 11.533 to -4.334 h. This means that, on average, time to first request for analgesia was 7.934 h longer in the 0.25% levobupivacaine group compared with the 0.0625% levobupivacaine group."

[Item 8, Vol. 1.68, p. 061 -062]

"There was no statistically significant difference between the 0.0625% levobupivacaine treatment group and the 125% levobupivacaine treatment group with respect to time to first request for analgesia (p=0.60). The estimate of the difference between the treatments (0.0625% levobupivacaine - 0.125% levobupivacaine) was -1.007 h, and the 95% confidence interval was -4.844 to 2.831 h."

"The secondary analysis performed for the per-protocol population showed the same overall results. However, the hazard ratio estimates changed slightly to 1.983 and 3.872 for the 0.125% levobupivacaine treatment group *vs* the 0.25% levobupivacaine treatment group and the 0.0625% levobupivacaine treatment group *vs* the 0.25% levobupivacaine treatment group respectively."

The statistical reviewer of this NDA submission has calculated the proportion of patients requesting analgesia and found a significantly lower number of patients in the 0.25% levobupivacaine requesting rescue medication than the other two treatment groups.

[Item 8, Vol. 1.68, pp. 062-063]

Table 86. Analysis of Primary Efficacy Measurement

TABLE 13 LEVOBUPIVACAINE - 030475

Summary and analysis (ANOVA) of time to first request for analgesia

by treatment group

Intent-to-treat population

Analgesia		Levobupivacaine 0.0625% (n=32)	Levobupivacaine 0.125% (n=27)	Levobupivacaine 0.25% (n=32)
Time (hrs) to first request	mean	8.106	9.506	16.664
	sd	4.979	6.950	8.324
	minimum	1.40	2.00	1.17
	maximum	24.00	24.00	24.00
	n	32	27	32
	missing	0	0	0

Statistical assessments

Pairwise comparison:	p-value (sig. level)#	mean estimate of treatment differences	95% C.I.s
0.0625% Levobupivacaine - 0.125% Levobupivacaine	0.49 (NS)	-1.231 hours	(-4.828, 2.365)
0.125% Levobupivacaine - 0.25% Levobupivacaine	<0.001 (*)	-6.888 hours	(-10.521, -3.255)
0.0625% Levobupivacaine - 0.25% Levobupivacaine	<0.001 (*)	-8.120 hours	(-11.587, -4.652)

NB: Time to first dose of relief medication for patients not requesting relief medication during the extradural infusion was the duration of the extradural infusion

Significance level of t-test following sequentially rejective Bonferroni-Holm adjustment

* Pairwise comparison significant at 5% level

NS Pairwise comparison not significant at 5% level

[Sponsor's Table 13, Item 8, Vol. 1.68, p. 110]

Table 87. Analysis of Primary Efficacy Measurement (continued)

TABLE 14 LEVOBUPIVACAINE - 030475

Summary and analysis (ANOVA) of time to first request for analgesia

by treatment group

Per-protocol population

Analgesia		Levobupivacaine 0.0625% (n=28)	Levobupivacaine 0.125% (n=21)	Levobupivacaine 0.25% (n=27)
Time (hrs) to first request	mean	7.482	8.624	15.852
	sd	4.531	6.642	8.474
	minimum	1.40	2.00	1.17
	maximum	24.00	24.00	24.00
	n	28	21	27
	missing	0	0	0
Statistical assessments				
Pairwise comparison :		p-value (sig. level)#	mean estimate of treatment differences	95% C.I.s
0.0625% Levobupivacaine - 0.125% Levobupivacaine		0.60 (NS)	-1.007 hours	(-4.844, 2.831)
0.125% Levobupivacaine - 0.25% Levobupivacaine		<0.001 (*)	-6.927 hours	(-10.823, -3.030)
0.0625% Levobupivacaine - 0.25% Levobupivacaine		<0.001 (*)	-7.934 hours	(-11.533, -4.334)

NB: Time to first dose of relief medication for patients not requesting relief medication during the extradural infusion was the duration of the extradural infusion

\# Significance level of t-test following sequentially rejective Bonferroni-Holm adjustment

* Pairwise comparison significant at 5% level

NS Pairwise comparison not significant at 5% level

[Sponsor's Table14, Item 8, Vol. 1.68, p. 111]

APPEARS THIS WAY
ON ORIGINAL

Table 88. Analysis of Primary Efficacy Measurement (continued)

TABLE 15.1 LEVOBUPIVACAINE - 030475

Summary and analysis (survival analysis) of time to first request for analgesia

by treatment group

Intent-to-treat population

Analgesia		Levobupivacaine 0.0625% (n=32)	Levobupivacaine 0.125% (n=27)	Levobupivacaine 0.25% (n=32)
Time (hrs) to first request (including censored patients)	25th percentile	4.73	3.25	9.53
	median	7.92	8.17	23.33
	75th percentile	10.13	12.42	24.00
	90th percentile	12.17	23.83	24.00
	interquartile range	5.4	9.2	14.5
	n	32	27	32
Censored patients	uncensored observations	31 (96.9%)	24 (88.9%)	17 (53.1%)
	censored observations	1 (3.1%)	3 (11.1%)	15 (46.9%)
Time (hrs) to first request (not including censored patients)	25th percentile	4.72	3.17	7.00
	median	7.83	7.96	9.58
	75th percentile	10.42	9.89	12.75
	90th percentile	12.17	15.15	23.17
	interquartile range	5.7	6.7	5.8
	n	31	24	17

NB: Censored patients are defined to be those patients who did not require relief medication during the extradural infusion
For censored patients, time to first dose of relief medication has been taken as the duration of the extradural infusion

[Sponsor's Table 15.1, Item 8, Vol. 1.68, p. 111]

Table 89. Analysis of Primary Efficacy Measurement (continued)

TABLE 15.2 LEVOBUPIVACAINE - 030475

Summary and analysis (survival analysis) of time to first request for analgesia

Statistical assessments

Intent-to-treat population

Statistical assessments	p-value (sig. level)#		Hazard ratio estimate of treatment differences	95% C.I.
Wilcoxon two-sample test :				
0.0625% Levobupivacaine v 0.125% Levobupivacaine				
'Centre' as a prognostic factor	0.19	(NS)		
'Surgery type' as a prognostic factor	0.80	(NS)		
Cox's proportional hazard models :				
0.125% Levobupivacaine / 0.25% Levobupivacaine	<0.001	(*)	1.791	(1.296, 2.475)
0.0625% Levobupivacaine / 0.25% Levobupivacaine	<0.001	(*)	4.181	(2.210, 7.907)

Significance level following sequentially rejective Bonferroni-Holm adjustment
* Significant at 5% level
NS Not significant at 5% level

[Sponsor's Table 15.2, Item 8, Vol. 1.68, p.113]

Table 90. Analysis of Primary Efficacy Measurement (continued)

TABLE 16.1 LEVOBUPIVACAINE - 030475

Summary and analysis (survival analysis) of time to first request for analgesia

by treatment group

Per-protocol population

Analgesia		Levobupivacaine 0.0625% (n=28)	Levobupivacaine 0.125% (n=21)	Levobupivacaine 0.25% (n=27)
Time (hrs) to first request (including censored patients)	25th percentile	4.48	3.08	8.08
	median	7.08	8.08	15.50
	75th percentile	9.83	10.00	24.00
	90th percentile	12.17	19.02	24.00
	interquartile range	5.4	6.9	15.9
	n	28	21	27
Censored patients	uncensored observations	27 (96.4%)	19 (90.5%)	15 (55.6%)
	censored observations	1 (3.6%)	2 (9.5%)	12 (44.4%)
Time (hrs) to first request (not including censored patients)	25th percentile	4.25	2.77	4.67
	median	6.33	7.83	9.58
	75th percentile	9.83	9.78	12.75
	90th percentile	12.17	12.42	15.50
	interquartile range	5.6	7.0	8.1
	n	27	19	15

NB: Censored patients are defined to be those patients who did not require relief medication during the extradural infusion
For censored patients, time to first dose of relief medication has been taken as the duration of the extradural infusion

[Sponsor's Table 16.1, Item 8, Vol. 1.68, p.114]

Table 91. Analysis of Primary Efficacy Measurement (continued)

TABLE 16.2

LEVOBUPIVACAINE - 030475

Summary and analysis (survival analysis) of time to first request for analgesia

Statistical assessments

Per-protocol population

Statistical assessments	p-value (Sig. level)#		Hazard ratio estimate of treatment differences	95% C.I.
Wilcoxon two-sample test :				
0.0625% Levobupivacaine v 0.125% Levobupivacaine				
'Centre' as a prognostic factor	0.19	(NS)		
'Surgery type' as a prognostic factor	0.18	(NS)		
Cox's proportional hazard models :				
0.125% Levobupivacaine / 0.25% Levobupivacaine	<0.001	(*)	1.983	(1.360, 2.892)
0.0625% Levobupivacaine / 0.25% Levobupivacaine	<0.001	(*)	3.872	(1.946, 7.706)

\# Significance level following sequentially rejective Bonferroni-Holm adjustment
* Significant at 5% level
NS Not significant at 5% level

[Sponsor's Table 16.2, item 8, Vol. 1.68, p. 115]

econdary Efficacy Measurement:

Normalized Dose of Morphine Administered

"For those patients in the intent-to-treat population, the median normalised dose of morphine was highest in the 0.0625% levobupivacaine treatment group at 1.50 mg per hour. Patients in the 0.125% levobupivacaine treatment group received a median morphine dose of 0.96 mg per hour while those in the 0.25% levobupivacaine treatment group received 0.21 mg per hour."

"Following a Bonferroni-Holm adjustment, the pairwise comparisons detected significantly lower normalised dose of morphine in the 0.25% levobupivacaine group compared with both 0.125% and 0.0625% levobupivacaine ($p=0.003$, $p<0.001$ respectively). The median estimate of treatment difference obtained between the 0.125% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group (0.125% levobupivacaine - 0.25% levobupivacaine), based on Wilcoxon's two-sample test was 0.583 mg per hour with a 95% confidence interval of 0.250 to 0.958 mg per hour. The median estimate of treatment difference between the 0.0625% levobupivacaine treatment group and the 0.25% levobupivacaine group (0.0625% levobupivacaine -0.25% levobupivacaine) was 0.963 mg per hour, and the 95% confidence interval was 0.542 to 1.702 mg per hour. This means that, on average, the 0.125% levobupivacaine patients requested 0.583 mg per hour more morphine than those patients in the 0.25% levobupivacaine group did. Similarly, the 0.0625% levobupivacaine group requested, on average, 0.963 mg per hour more morphine than the 0.25% levobupivacaine group."

"The pairwise comparison between the 0.0625% levobupivacaine treatment group and the 0.125% levobupivacaine treatment group did not produce a significant difference ($p=0.16$). However, the median stimate of treatment difference was 0.417 mg per hour (0.0625% levobupivacaine - 0.125% levobupivacaine) th 95% confidence interval of-0.083 to 1.087 mg per hour.

[Item 8, Vol. 1.68, pp. 063 - 064]

Normalized Number of Requests for Morphine via PCA Pump

For the intent-to-treat population, the median normalised number of requests for morphine was lowest in the 0.25% levobupivacaine treatment group with 0.00 requests per hour *(ie* at least 50% of the patients in the 0.25% levobupivacaine treatment group did not request morphine *via* the PCA pump). Patients in the 0.0625% levobupivacaine treatment group had a median value of 1.46 requests per hour and those in the 0.125% levobupivacaine treatment group had a median value of 1.48 requests per hour."

"Following a Bonferroni-Holm adjustment, the pairwise comparisons detected significantly lower normalised number of requests for analgesia in the 0.25% levobupivacaine group compared with both 0.125% and 0.0625% levobupivacaine ($p \leq 0.001$ in both cases). The median estimate of treatment difference obtained between the 0.125% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group (0.125% levobupivacaine - 0.25% levobupivacaine), based on Wilcoxon' s two-sample test was 0.917 requests per hour with a 95% confidence interval of 0.458 to 2.122 requests per hour. The median estimate of treatment difference between the 0.0625% levobupivacaine treatment group and the 0.25% levobupivacaine group (0.0625% levobupivacaine - 0.25% levobupivacaine) was 1.292 requests per hour, and the 95% confidence interval was 0.625 to 2.447 requests per hour. This means that, on average, the 0.125% levobupivacaine patients reported 0.917 more requests per hour than those patients in the 0.25% levobupivacaine group. Similarly, the 0.0625% levobupivacaine group reported, on average, 1.292 more requests per hour than the 0.25% levobupivacaine group."

"There was no statistically significant difference between the 0.125% and 0.0625% levobupivacaine groups ($p=0.72$) with respect to normalised number of requests."

[Item 8, Vol. 1.68, pp. 064 - 065]

Visual Analogue Pain Scale

After 1 h, the VAS scores increased to a peak and then decreased. In the 0.0625% levobupivacaine treatment group the decrease began at 12 h. The VAS scores in the 0.125% levobupivacaine treatment group increased steadily from 1 h to 10 h and then decreased and increased alternately between 10 h and 24 h. The VAS scores in the 0.25% levobupivacaine treatment group did not begin to increase till 4 h post dose, peaked at 18 h and then decreased. The height of the peak was less than in either of the other 2 treatment groups."

"Generally, the 0.25% levobupivacaine treatment group had the lowest mean VAS pain score and the 0.0625% levobupivacaine treatment group had the highest mean VAS pain scores."

"The mean VAS scores until analgesia can be seen that the 0.25% levobupivacaine treatment group had the lowest VAS pain scores between 1 h and 24 h following the extradural infusion. However, this time, the graph shows that the treatment group with the highest VAS pain scores seemed to alternate between the 0.0625% levobupivacaine treatment group and the 0125% levobupivacaine treatment group for each timepoint. The 0.0625% levobupivacaine treatment group had large changes in VAS pain scores between 10 h, 12 hand 18 h, resulting in a large peak (48 mm) at 12 h. The peak should be viewed in the context of the low number of patients in the 0.0625% levobupivacaine treatment group at those particular timepoints."

Height of Sensory Block

"For the left and right upper dermatomes the variation between the treatments was small. The median segmental levels of sensory block appeared to decrease exponentially with time, between LI and TI. The left and right lower dermatomes did not show much variation between treatments either. However, the median segmental levels appeared to remain constant over all assessments, between LS and LI.

em 8, Vol. 1.68, pp. 066 - 067]

'otor Block

There were many missing values for timepoints 1 h and 2 h following the extradural infusion. This was a result of the patients still being asleep after the operation.

The histogram also shows that the 0.125% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group were similar in the percentage of patients with motor block grades 1 and 3, but that the 0.125% levobupivacaine treatment group had more patients with grade 0 and less patients with grade 2 than the 0.25% levobupivacaine treatment group.

The pairwise analysis of the maximum grade of motor block achieved for the 0.0625% levobupivacaine treatment group and the 0.125% levobupivacaine treatment group satisfied the proportional odds assumption (p=0.30). An odds ratio of 3.972 was calculated (p=0.012) with 95% confidence interval of 1.356 to 11.637 (ie following a Bonferroni-Holm adjustment, the odds of decreased motor block is significantly higher in the 0.0625% levobupivacaine group compared with the 0.25% levobupivacaine group). Interpretation of these results indicated that patients in the 0.0625% levobupivacaine treatment group were 3.972 times more likely to have less motor block than patients in the 0.125% levobupivacaine treatment group.

The pairwise analysis of the maximum grade of motor block achieved for the 0.0625% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group also satisfied the proportional odds assumption. Again after a Bonferroni-Holm adjustment, a statistically significant difference between the 2 treatments was detected (p<0.001). An odds ratio of 8.004 was calculated with 95% confidence interval of 2.750 to 23.291.

"The final pairwise analysis between the 0.125% levobupivacaine treatment group and the 0.25% levobupivacaine treatment group found no statistically significant difference between treatment groups (p=0.30). The odds ratio was 1.289 and the 95% confidence interval was 0.799 to 2.080. Interpretation of these results indicated that patients in the 0.125% levobupivacaine treatment group were 1.289 times as likely to have no paralysis as patients in the 0.25% levobupivacaine treatment group. However, the difference was not statistically significant."

[Item 8, Vol. 1.68, pp. 068 - 069]

Table 92. Analysis of Secondary Efficacy Measurement

TABLE 17.1

LEVOBUPIVACAINE - 030475

Summary and analysis of normalised morphine requirements

by treatment group

Intent-to-treat population

Variable		Levobupivacaine 0.0625% (n=32)	Levobupivacaine 0.125% (n=27)	Levobupivacaine 0.25% (n=32)
Normalised morphine requirements (mg)	mean	1.751	1.230	0.552
	median	1.50	0.96	0.21
	sd	1.323	0.930	0.691
	minimum	0.29	0.00	0.00
	maximum	5.72	4.13	2.38
	n	31	27	32
	missing	1	0	0
Normalised no. of requests for morphine	mean	2.445	2.065	0.535
	median	1.46	1.48	0.00
	sd	2.943	2.351	0.830
	minimum	0.13	0.00	0.00
	maximum	12.25	10.42	3.17
	n	29	26	31
	missing	3	1	1

NB: Patient 161 had infusion time greater than 25 hours, therefore this patient was treated as missing in the table

[Sponsor's Table 17.1, Item 8, vol. 1.68, p.116]

APPEARS THIS WAY
ON ORIGINAL

Table 93. Analysis of Secondary Efficacy Measurement (continued)

TABLE 17.2 LEVOBUPIVACAINE - 030475

Summary and analysis of normalised morphine requirements

Statistical assessments

Intent-to-treat population

Statistical assessments	p-value	(sig.level)#	median estimate of treatment differences	95% C.I.
Normalised dose of morphine administered test Wilcoxon two-sample:				
0.0625% Levobupivacaine - 0.125% Levobupivacaine	0.16	(NS)	0.417	(-0.083, 1.087)
0.125% Levobupivacaine - 0.25% Levobupivacaine	0.003	(*)	0.583	(0.250, 0.958)
0.0625% Levobupivacaine - 0.25% Levobupivacaine	<0.001	(*)	0.963	(0.542, 1.702)
Normalised number of requests for analgesia test Wilcoxon two-sample test :				
0.0625% Levobupivacaine - 0.125% Levobupivacaine	0.72	(NS)	0.458	(-0.333, 1.625)
0.125% Levobupivacaine - 0.25% Levobupivacaine	<0.001	(*)	0.917	(0.458, 2.122)
0.0625% Levobupivacaine - 0.25% Levobupivacaine	<0.001	(*)	1.292	(0.625, 2.447)

\# Significance level of Wilcoxon two-sample test following sequentially rejective Bonferroni-Holm adjustment
* Pairwise comparison significant at 5% level
NS Pairwise comparison not significant at 5% level

[Sponsor's Table 17.2, Item8, Vol. 1.68, p.117]

Table 94. Analysis of Secondary Efficacy Measurement

TABLE 22.1

LEVOBUPIVACAINE - 030475

Summary and analysis of maximum grade of motor block achieved

by treatment group

Intent-to-treat population

Maximum grade of motor block	Levobupivacaine 0.0625% (n=32)	Levobupivacaine 0.125% (n=27)	Levobupivacaine 0.25% (n=32)
No paralysis, full flexion of knee and ankle	22 (68.8%)	12 (44.4%)	9 (28.1%)
Inability to raise extended leg, able to move knee	7 (21.9%)	5 (18.5%)	6 (18.8%)
Inability to flex knee, able to flex ankle	1 (3.1%)	3 (11.1%)	10 (31.3%)
Inability to move lower limb	2 (6.3%)	7 (25.9%)	7 (21.9%)
Motor block not assessed throughout assessment period	0	0	0

[Sponsor's Table 22.1, Item 8, Vol. 1.68, p.156]

Table 95. Analysis of Secondary Efficacy Measurement (continued)

TABLE 22.2

LEVOBUPIVACAINE - 030475

Summary and analysis of maximum grade of motor block achieved

Statistical assessments

Intent-to-treat population

Statistical assessments	p-value	(sig. level)#	odds ratio	95% C.I.
Logit Model :				
0.0625% Levobupivacaine / 0.125% Levobupivacaine	0.012	(*)	3.972	(1.356, 11.637)
0.125% Levobupivacaine / 0.25% Levobupivacaine	0.30	(NS)	1.289	(0.799, 2.080)
0.0625% Levobupivacaine / 0.25% Levobupivacaine	<0.001	(*)	8.004	(2.750, 23.291)

\# Significance level following sequentially rejective Bonferroni-Holm adjustment
* Significant at 5% level
NS Not Significant at 5% level

[Sponsor's Table 22.2, Item 8, Vol. 1.68, p.157]

REVIEWER'S EFFICACY DISCUSSION

The primary efficacy variable - mean time to the first request for analgesia - was highest in the 0.25% levobupivacaine treatment group at 16.664 h compared with 8.106 h in the 0.0625% levobupivacaine treatment group and 9.506 h in the 0.125% levobupivacaine treatment group. ($p<0.001$).

There was no statistically significant difference between the 0.0625% levobupivacaine treatment group and the 0.125% levobupivacaine treatment group with respect to time to first request for analgesia ($p=0.49$). This trend was also seen in the analysis of the secondary variables – normalized dose of morphine, VAS scores and extent of motor block, i.e., levobupivacaine like bupivacaine demonstrates a concentration effect.

The analysis of the secondary variable - height of sensory block – showed small variations between the treatment groups.

Overall, the clinical data shows that the product, levobupivacaine, is effective when administered as an epidural infusion in concentrations of 0.0625%, 0.125% and 0.25% to patients following orthopedic surgery. This conclusion is based upon the evidence that patients admitted to some level of analgesia following epidural infusion for post-orthopedic surgery.

STUDY # CS-004

PROTOCOL SYNOPSIS:

Title: "Double-Blind Randomized Controlled Trial to Assess the Efficacy of 0.25% Levobupivacaine Combined with 0.005% Morphine, 0.25% Levobupivacaine Alone or 0.005% Morphine Alone for Post-operative Pain in Patients Undergoing Major Abdominal Surgery"

Primary Objective: "...to assess the analgesic effect of 0.25% Levobupivacaine when combined with 0.005% morphine."

Secondary Objective: "...to assess the volume of rescue analgesia required in the 24-hour post-operative period (both study drug infusion and additional pain control with ketorolac); to assess motor block and pain (VAS) at various time points; to evaluate the relative safety and efficacy profiles of the three different treatment groups"

[item 8, Vol. 1.72, p. 004]

Study Design:

The study is designed as a randomized, multi-center, double-blind, 3 arm parallel group comparative study of 0.25% levobupivacaine, 0.25% levobupivacaine / 0.005% morphine, and 0.005% morphine. Patients were randomized using a 1:1:1 allocation.

Group I	0.25% levobupivacaine
Group II	0.25% levobupivacaine / 0.005% morphine
Group III	0.005% morphine

Eligible patients were male/female of normal weight and height, between 18 and 80 years of age (inclusive), ASA Class I - III, who consented to receive a combination general/epidural anesthetic for major abdominal surgery. Patients with history of stomach ulcers, systemic illness, drug or alcohol abuse within six months prior to study entry, participation in a clinical trial in the previous month or were pregnant/lactating, or currently receiving treatment with beta-blockers were excluded from participation.

Eligible patients, from two separate study sites, fasted for 8 hours prior to surgery. Also pre-operatively, they received midazolam (0.5–4.0 mg), a saline infusion and iv antibiotics, prophylactically.

On the day of surgery, the patient underwent an epidural anesthetic with 6 –12 ml of 0.75% levobupivacaine. Initially, a test dose of 3 ml of 1.5% lidocaine with 15 ug of epinephrine was given. If after 5 minutes, there was no evidence of intravascular of subarachnoid injection, the 6-12 ml of 0.75% levobupivacaine was administered (rate not specified).

If inadequate sensory block was assessed 15 minutes after injection, one additional injection of 5 ml of 0.75% levobupivacaine was administered. If after an additional 45 minutes, inadequate sensory block was assessed, the patient was withdrawn and received alternate anesthesia.

General anesthesia was then induced with propofol or etomidate with dose titration to loss of consciousness and was maintained with sevoflurane or isoflurane. At the discretion of the investigator, neuromuscular blocking agents were used to facilitate endotracheal intubation and intra-operative muscle relaxation.

At the end of surgery, all patients were given a bolus of 2 ml of blinded medication via the epidural catheter, i.e., 2 ml of 0.1% morphine (2mg) for the two groups randomized to receive morphine and 2 ml of saline to the levobupivacaine group. This was followed by the randomized study drug infusion (Time 0) which was maintained for 24-hours postoperatively. The infusion consisted of either 0.25% levobupivacaine combined with 0.005% morphine, 0.25% levobupivacaine alone or 0.005% morphine alone.

At the end of the 24-hour infusion period, patients were given alternative continuous epidural analgesia or intravenous patient-controlled analgesia, as needed for post-operative pain. If the initial epidural infusion failed to provide adequate analgesia, the patient received additional medication according to the following regimen:

A) A loading dose of 4 ml of study medication was given and the infusion was increased by 2 ml to 6 ml/hr;
B) If analgesia remained inadequate within one hour, an additional 6 ml of study medication was given, and the infusion rate was increased by 2 ml/hr to 8 ml/hr;
C) If within one additional hour, the patient was still experiencing pain, an additional loading dose of 8 ml was given and the infusion rate was increased by 2 ml/hr to 10 ml/hr.

At any time after the initial loading dose and increase in infusion rate (A)1, ketorolac (15-30 mg) was administered as a supplemental analgesic. Patients aged < 60 years were allowed to receive up to 30 mg of ketorolac every 6 hours; patients aged > 60 years were restricted to 15 mg every 6 hours.

The primary efficacy endpoint was the time to first verbal request for rescue analgesia in the 24-hour post-operative period. The secondary endpoints were: (1) volume of epidural rescue analgesia required in the 24-hour, (2) request for and administration of ketorolac, (3) severity of pain, and, (4) time to achievement and duration of sensory and motor block.

Sensory block was assessed at 0, 2, 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes or until an appropriate block was achieved, i.e., T4 – L1 for upper abdominal surgery and T6 – L4 for lower abdominal surgery. Motor block was assessed using a modified Bromage scale at 0, 10, 20 and 30 minutes or until a score of 3 was achieved. Pain was assessed, using the Visual Analog Scale, when the patient was at rest and when coughing. This assessment were made at Time 0, and at 4, 8, 12, 16, and 24 hours.

Both the patient and the investigator completed the global VAS rating for overall plan satisfaction at the end of the trial.

Table 96. Schedule of Assessments

8.2 Patient Evaluation Schedule

The assessments performed during the study are presented below in Table 2.

Table 2 Patient Evaluation Schedule

Study Parameter	Pre-Study	Pre-Surgery	Surgery	Post-Surgery
History and Consent	X			
Physical Exam[1]	X			
12-lead ECG	X			X
Vital Signs	X		Every 30 minutes	4, 8, 12, 16, 20, and 24 hrs
Epidural Anesthesia		X	X[2]	
Study Medication				X[3]
Rescue/Escape Analgesia				X[4]
Sensory Block		0, 2, 5, 10, 15, 20, 25, 30, 40, 50, 60 minutes or until an appropriate block is achieved		4, 8, 12, 16, 20, and 24 hrs
Motor Block (Bromage scale)		Time 0, 10, 20, and 30 minutes or until a score of 3 is achieved		4, 8, 12, 16, 20, and 24 hrs
VAS Pain Rating (at rest and when the patient coughs)				Time 0, 4, 8, 12, 16, 20 and 24 hrs[5]
Clinical Laboratory Sampling	X			X
Adverse Events	X	X	X	X[6]

[1]Includes body weight and height and urine or serum pregnancy test for women of childbearing potential. [2]Possible top-up dose at Investigator discretion. [3]Bolus dose with continuous infusion until 24-hours post surgery. [4]At the Investigators discretion up to 3 additional loading doses and increased infusion rate of study drug may be administered following the initial bolus dose before administration of ketorolac. [5]Global VAS rating for overall pain at the end of the study will be completed by both the patient and investigator. [6]Within 3-7 days post-discharge to determine residual effects of the study drug.

[Sponsor's Table 2, "Patient Evaluation Schedule", Item 8, Vol. 1.72, p.032]

STATISTICAL ANALYSIS

The Intent-to-Treat population was defined as all randomized patients excluding those who did not receive the randomized anesthetic and who experienced an intravascular or subarachnoid injection resulting in immediate withdrawal from the study.

"All efficacy analyses were done on the ITT population. The key comparison was between the morphine and levobupivacaine plus morphine groups. This comparison used a two-sided test with an alpha level of 0.05. There was no significance level adjustment for multiple comparisons."

"In the survival analysis and the analysis for rates for the pairwise comparisons, the data from the group that was not involved in the comparison were excluded. In the analysis for means for the pairwise comparisons, the appropriate contrasts were utilized in the analysis variance. The center effect was adjusted for all analyses."

Primary Efficacy Analyses

"The primary parameter was the time to first verbal request for rescue analgesia. A survival analysis using the product-limit (Kaplan-Meier) approach with study drug as a treatment factor was used to analyze onset of time to first administration of rescue medication. The centers were used as a stratification factor in the model. Pairwise comparisons were generated by analyzing only two treatment groups."

[Item 8, Vol. 1.72, pp. 037–038]

:condary Efficacy Analyses

"The volume of study drug administered in the 24-hour postoperative period, the amount of ketorolac administered in the 24-hour postoperative period, the post-surgery motor block at six time points, the post-surgery VAS assessments at rest and when the patient coughed, and the global VAS assessments by patients and by investigator were analyzed by the analysis of variance with factors of treatment, center, and their interaction. SAS Type III estimable functions were used. The adjusted means and confidence interval were based on the pairwise least squares means from this model. If appropriate, a transformation (e.g., arcsine), logistic regression, or non-parametric statistic was used. The dichotomous parameters, usage of ketorolac and proportion of patients who requested rescue medication, were analyzed by a Cochran-Mantel-Haenszel test controlling for center. The confidence interval for the difference between proportions was generated by equation 2.14 from Fleiss.[6] Pairwise differences were determined when only the relevant treatment groups were present."

"Time to onset of sensory block adequate for surgery was derived and defined as the time when the maximum of the left or right lower blocks was at or below L4 and the minimum of the left or right upper blocks was at or above T10. If both of these criteria were never reached, then time to onset was defined as the start time of surgery."

"Maximum spread of post-surgery sensory block was defined as the number of dermatomes between the upper and lower sensory blocks (difference plus one). If the left and right sides had a difference in upper dermatomes, then the higher side was used. If the left and right sides had a difference in lower dermatomes, then the lower side was used."

"Item 8, Vol. 1.72, pp. – 038 -039]

PROTOCOL AMENDMENT:

This amendment was dated 5/28/97. It consists of the following changes:

A. New Exclusion Criteria
- Patients who are currently receiving beta-blockers have been excluded from study participation. This decision was based upon a "Safety Report" submitted to the FDA on June 5, 1997. This decision has since been retracted; however, patient accrual had already ended. Therefore, patients on beta-blockers were excluded from participation.

B. Follow-up Procedures -
- Revised to include a more detailed description of the follow-up procedure. An example of the questions to be asked has been included, as well as the plan for adverse events.

C. Case Report Form
- A statement concerning medications used post-operatively and their recording on the CRF has been revised to include all medications given post-operatively until hospital discharge or 7 days post end of infusion.

CONDUCT OF STUDY

Patient Distribution/Disposition:

A total of 68 patients were randomized from two treatment sites into three treatment groups: 22 patients in the 0.75% levobupivacaine/morphine group, 23 in the 0.75% levobupivacaine group and 23 in the 0.005% morphine group. Of the 68 patients randomized, 66 (97.0) received study medication and were included in the safety population.

Two patients (No. 002-01 randomized to levobupivacaine and No. 004-01 randomized to the combination) discontinued prior to receiving 0.75% levobupivacaine as pre-operative anesthesia. All 66 remaining patients were considered evaluable for safety.

Two patients (No. 111-02 randomized to morphine and No 125-02 to levobupivacaine) received 0.75% levobupivacaine as pre-surgical anesthesia but were excluded from the Intent-to-Treat population. The remaining 64 patients (94.1%) were included in the ITT population. The Intent-to-Treat population was defined as all randomized patients who received the randomized anesthetic and who did not experienced an intravascular or subarachnoid injection resulting in immediate withdrawal from the study.

Four patients (No. 102 - 02 [morphine], 103-02 [levobupivacaine], 104-02 [levobupivacaine], and 126-02 [morphine]) received continuous infusions of fentanyl or remifentanil as anesthesia during surgery and were excluded from the per-protocol population. The remaining 60 patients were included in the per-protocol population. The criteria for defining the per-protocol population were determined by the Medical Director or designee at Chiroscience prior to unblinding of the study.

Twenty-four patients discontinued before the end of the 24-hour post-operative study period and 44 patients completed the study.

Table 97. Patient – Specific Protocol Violations

PATIENT NUMBER/CENTER	TREATMENT GROUP	VIOLATION	PATIENT TOTALS N (%)
			68 (100) Randomized
Excluded from Safety Population:			**66 (97.1) Safety Population**
002/01	Levobupivacaine (Not Treated)	Surgery Rescheduled	
004/01	Combination (Not Treated)	Height Violation	
Excluded from Intent-to-Treat:		Adequate Sensory Block Not Achieved 15 min After Additional Injection	**64 (94.1) Intent-to-Treat**
111/01	0.75% Levobupivacaine		
125/02	0.75% Levobupivacaine		
Excluded from Per-Protocol:			**60 (88.2) Per-Protocol**
103 and104/02;	0.25% Levobupivacaine	Given Prohibited Narcotic Intra-Operatively (Remifentanil/Fentanyl)	
102 and 126/02	0.005% Morphine		
Other Discontinuations:			
106, 119, 124 and 108/02; 031/01	Morphine	Pain Not Controlled by Concomitant Ketorolac	
114, 107,117,120,132, 110/02; 011, 008/01	0.25% Levobupivacaine		
123/02	0.25% Levobupivacaine	Patient with Discomfort Prior to Next Scheduled Ketorolac, Hypotension	
027/01	0.25% Levobupivacaine	Excessive Motor Block and Pain	
134/02	0.25% Levobupivacaine	Patient Request Discontinuation – Inadequate Pain Relief with Epidural	
133/02	Combination	Asystole	
007	0.005% Morphine	Hypotension	
012	0.005% Morphine	Post-Operative Cardio-Respiratory Instability	
24 (35.3 %) Total Withdrawals			**44 (64.7) Total Completed[5]**

[5] Patient Nos. 103, 126 and 104 completed the study; i.e., were not withdrawals, however, they were not included in the per-protocol population.

Table 98. Patient Disposition

Table 3 Patient Disposition

Patients	Levobupivacaine/ Morphine N (%)	Levobupivacaine N (%)	Morphine N (%)	All Patients N (%)
Randomized	22 (100)	23 (100)	23 (100)	68 (100)
Safety Population	21 (95.5)	22 (95.7)	23 (100)	66 (97.1)
ITT Population	21 (95.5)	21 (91.3)	22 (95.7)	64 (94.1)
Per-Protocol Evaluable	21 (95.5)	19 (82.6)	20 (87.0)	60 (88.2)
Total Discontinued	2 (9.1)	13 (56.5)	9 (39.1)	24 (35.3)
Total Completed	20 (90.9)	10 (43.5)	14 (60.9)	44 (64.7)

Abstracted from Statistical Table 1

[Sponsor's Table 3., Item 8, Vol. 1. 72, p. 041]

Note: In "Data Listing 16" pp. 375 – 380, the total completed differs from the totals seen in the sponsor's "Table 3" above. According to the Data Listings, the number of discontinued patients in the levobupivacaine group (includes both 0.75 Levobupivacaine and 0.25% Levobupivacaine) is 14 and the number of discontinued patients the morphine group is 8.

The protocol states that if at any time following the initial loading dose of 0.75% levobupivacaine and increase in infusion rate of the randomized drug, ketorolac may be administered as a supplemental analgesic. The study results showed that the majority (13/24, 54.1%) of terminations was due to inadequate pain control. Additionally, of all the patients treated, the majority of withdrawals occurred in those patients treated with 0.25% levobupivacaine alone (13/66, 19.7%) or 0.005% morphine alone (9/66, 13.6%) versus the combination therapy, 0.25% levobupivacaine/0.005% morphine. There was only one patient in the combination treatment group who was withdrawn and in that case it was secondary to asystole.

"Eleven (52.4%) of the 21 patients who received levobupivacaine alone discontinued prior to completion *[Note: Table 3 shows that there were 13 patients, although my count is 14, who received levobupivacaine alone and 22 patients who received levobupivacaine alone]*, eight (36.4%) of the 22 patients who received morphine alone *[Note: Table 3 shows that there were 9 patients, I believe that there were 8, based upon the "Data Listings"]*, and one (4.8%) of 21 patients who received the combination discontinued prematurely."

[Item 8, Vol. 1.72, p. 041-42]

Demographics

ne following table summarizes the demographic characteristics of the three treatment groups:

Table 99. Demographics - Intent-to-Treat Population

Table 4 Patient Demographics and Baseline Characteristics: Intent-To-Treat Population

Variable	Levobupivacaine/ Morphine	Levobupivacaine	Morphine	All Patients
Sex N (%)				
Male	13 (61.9)	10 (47.6)	11 (50.0)	34 (53.1)
Female	8 (38.1)	11 (52.4)	11 (50.0)	30 (46.9)
Race N (%)				
Caucasian	16 (76.2)	15 (71.4)	17 (77.3)	48 (75.0)
Black	5 (23.8)	6 (28.6)	4 (18.2)	15 (23.4)
Hispanic	0	0	1 (4.5)	1 (1.6)
Age (years)				
Mean ± S.D.	48.8 ± 9.55	48.8 ± 14.87	56.2 ± 13.27	51.3 ± 13.05
Median	49.0	46.0	55.5	51.0
Minimum	28	25	32	25
Maximum	70	75	79	79
Weight (kg)				
Mean ± S.D.	78.64 ± 11.28	79.61 ± 15.98	75.67 ± 12.72	77.94 ± 13.35
Median	76.40	79.10	78.20	77.15
Minimum	59.0	56.0	47.0	47.0
Maximum	99.5	107.7	101.0	107.7

Abstracted from Statistical Table 3.2.

[Sponsor's Table 4., Item 8, Vol.1.72, p. 042]

The percentages of male and female were similar, i.e., 53% male and 47% female. The majority of patients were Caucasian (76%), with a mean age of 52 years and weight of 78 kilograms.

The overall medical histories at screening, were significant and included such illnesses as genitourinary cancer(with or without metastasis), diabetes mellitus, Crohn's disease, and pancreatitis.

Concomitant medications administered included pre-operative sedatives, nausea prophylaxis, anesthetics and anesthetic reversal agents, vasopressors and pain medications, most commonly. There were 19 protocol deviations involving the use of concomitant medications. The majority of these involved the use of fentanyl and/or thiopental as an adjunct during induction of anesthesia. The four major infractions involved the continuous infusion of remifentanil or fentanyl during maintenance of anesthesia.

Table 101. Analysis of Secondary Variable

Table 7 Proportion of Patients Who Requested Rescue Analgesia

	Levobupivacaine/ Morphine N = 21 n (%)	Levobupivacaine N = 21 n (%)	Morphine N = 22 n (%)
Requested rescue analgesic medication	10 (47.6)	20 (95.2)	16 (72.7)
Did not request rescue analgesic medication	11 (52.4)	1 (4.8)	6 (27.3)

Pairwise Comparisons	95% Confidence Interval	p-value
Combination versus Morphine	-0.251 (-0.581, 0.079)	0.062
Levobupivacaine versus Morphine	+0.225 (NE, NE*)	0.044
Combination versus Levobupivacaine	-0.476 (NE, NE)	<0.001

*Not estimable due to small sample size. Abstracted from Statistical Table 7.3.

[Sponsor's Table 7, Item 8, Vol. 1.72, p. 045]

Table 102. Analysis of Secondary Variable

Table 8 Amount (mL) of Rescue Study Medication Administered in 24-Hour Post-Operative Study Period

Amount (mL)	Levobupivacaine/ Morphine N = 21	Levobupivacaine N = 21	Morphine N = 22
Adjusted mean	115.28	122.11	103.42
Arithmetic mean ± S.D.	116.3 ± 39.71	121.68 ± 52.38	103.42 ± 48.64
Median	97.10	121.70	97.65
Minimum	17.9	40.0	9.8
Maximum	194.4	229.4	197.5

Pairwise Comparisons	Mean Difference (95% Confidence Interval)	p-value
Combination versus Morphine	+11.86 (-17.22, 40.95)	0.418
Levobupivacaine versus Morphine	+18.69 (-10.26, 47.64)	0.201
Combination versus Levobupivacaine	-6.83 (-36.26, 22.61)	0.644

Abstracted from Statistical Table 7.5.

[Sponsor's Table 8. Item 8, Vol. 1.72, p.045]

Proportion of Patients who Requested Ketorolac and the Amount of Ketorolac Administered.

"The difference (30%) in the proportion of patients requesting ketorolac between the levobupivacaine/morphine combination group and the morphine group was statistically significant (p=0.040). For those requesting ketorolac, the amount of ketorolac administered did not differ significantly across treatment groups."

Table 103. Analysis of Secondary Variable

Table 9 Proportion of Patients Requesting Ketorolac

	Levobupivacaine/ Morphine N = 21 n (%)	Levobupivacaine N = 21 n (%)	Morphine N = 22 n (%)
Requested ketorolac	7 (33.3)	18 (85.7)	14 (63.6)
Did not request ketorolac	14 (66.7)	3 (14.3)	8 (36.4)

Pairwise Comparisons	Proportion Difference (95% Confidence Interval)	p-value
Combination versus Morphine	-0.303 (-0.634, 0.028)	0.040
Levobupivacaine versus Morphine	+0.221(NE*, NE)	0.090
Combination versus Levobupivacaine	-0.524 (NE, NE)	<0.001

*Not estimable due to small sample size. Abstracted from Statistical Table 8.1.

Table 10 Quantity of Ketorolac Administered During the 24-Hour post-Operative Study Period

Amount (mg)	Levobupivacaine/ Morphine N = 7	Levobupivacaine N = 18	Morphine N = 14
Adjusted mean	33.8	51.6	33.5
Arithmetic mean ± S.D.	34.3 ± 11.34	51.7 ± 30.53	35.4 ± 20.89
Median	30.0	52.5	30.0
Minimum	30	15	15
Maximum	60	120	90

Pairwise Comparisons	95% Confidence Interval	p-value
Combination versus Morphine	0.25 (-24.39, 24.89)	0.984
Levobupivacaine versus Morphine	18.12 (-1.11, 37.36)	0.064
Combination versus Levobupivacaine	-17.87 (-41.43, 5.58)	0.132

Abstracted from Statistical Table 8.2.

[Sponsor's Tables 9 and 10, Item 8, Vol. 1.72 p. 046]

Extent of Motor Block

The duration of post-surgery motor block was assessed every four hours after the completion of surgery until 24 hours post-operatively. At the four–hour time point, approximately 80% of all study patients had no lingering paralysis (i.e. a score of 0). At eight hours post-surgery, all patients with ratings were reported to have no paralysis and full movement of their legs."

Patient VAS at Rest and When Coughing

"VAS assessments were obtained every four hours after the completion of surgery until 24 hours post-operatively both when the patient was at rest and when the patient was coughing. At rest, the combination versus morphine comparison was statistically significant (p=0.001) at 8 hours, and approached significance at 20 hours (p=0.081) and 24 hours (p=0.101). While coughing, the combination versus morphine comparison was statistically significant at 4 hours (p=0.031) and 8 hours (p=0.029)."

Please refer to Appendix 7, Statistical Tables 10.1 and 10.2 for details.

Global VAS by Patient and Investigator

"At the end of the study, both patients and the investigators gave an overall assessment of their level of pain. Patients in all three treatment arms rated their overall pain score higher than did the investigators. From the patient ratings, difference between the combination and morphine groups was not statistically significant (p=0.167). However, according to the analysis performed by the statistical reviewer, the patient ratings of the difference between the combination and levobupivacaine demonstrated statistical significance p=0.029. The overall assessment of pain by the investigators was marginally significant for the combination versus morphine (p= 0.056)."

"Other parameters measured in this study included time to onset of sensory block adequate for surgery. The median time times to onset of sensory block were 9.0, 6.0 and 5.5 minutes for the combination, levobupivacaine, and morphine treatment groups, respectively. It should be noted that patients would have only received 0.75% levobupivacaine as pre-surgery anesthesia and would not have received the study drug."

[Item 8. Vol. 1.72 p. 046 – 047]

REVIEWER'S EFFICACY DISCUSSION

The primary efficacy variable - time to first verbal request for rescue study drug – favored the combination treatment group (levobupivacaine/morphine (p=0.066). The analysis of the secondary variables demonstrated the same trends, i.e., patients in the combination group requested less rescue medication than the single therapy treatment group (p=0.062).

Patients receiving the combination demonstrated: (1) statistically significant pain control at rest (at 8 hours) and while coughing (at 4 and 8 hours), (2) fewer requests for rescue analgesia and ketorolac (although of those requesting ketorolac, the amount administered did not differ statistically), and (3) higher patient global VAS score in contrast to the single therapy treatment groups.

Although the levobupivacaine group demonstrated lower rates of rescue medication administration, it was not found to be statistically significant. The mean volume of rescue medication administered was similar across treatment groups.

Of interest is the difference in bolus dosing between groups. Patients randomized to receive the combination therapy or morphine alone received a bolus of 2 mg of morphine and those patients randomized to the levobupivacaine group received saline. Although the bolus dose of morphine is less than the recommended dosage of epidural morphine (i.e., 5-7mg), it likely produced some level of analgesia greater than that seen from saline administration. This difference is weighs in favor of the comparator.

Overall, the clinical data shows that levobupivacaine's effectiveness is improved when administered as an epidural infusion in combination with 0.005% morphine to patients following major abdominal surgery. This conclusion is based upon the evidence that patients in the combination group more often admitted to analgesia than the other treatment groups. However, this has not been proven to be statistically significant.

STUDY # CS-006

PROTOCOL SYNOPSIS:

Title: "Double-blind Randomized Controlled Trial to Assess the Efficacy of 0.125% Levobupivacaine Combined with Fentanyl, 0.125% Levobupivacaine Alone or Fentanyl Alone Using patient Controlled Analgesia in Patients Undergoing Major Orthopaedic Surgery"

Primary Objective: "...to assess the analgesic efficacy of levobupivacaine when combined with fentanyl."

Secondary Objective: "...to assess the volume of rescue analgesia required in the 24-hour post-operative period; to assess motor block and pain (VAS) at various time points; to evaluate the relative safety and efficacy profiles of the three different treatment groups"

[item 8, Vol. 1.75, p. 019]