Study Design:

The study was designed as a randomized, multi-center, double-blind, 3 arm parallel group to examine the efficacy of 0.125% levobupivacaine, 0.125% levobupivacaine/fentanyl, and fentanyl. Patients were randomized using a 1:1:1 allocation.

Group I	0.125% levobupivacaine
Group II	0.125% levobupivacaine / 4ug/ml fentanyl
Group III	4ug/ml fentanyl

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 an epidural anesthetic for major orthopedic surgery. Patients with history of 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 scheduled for bilateral total hip or knee replacement were excluded from participation.

Eligible patients 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 maximum of 20 ml of 0.75% levobupivacaine. Initially a test dose of3ml of 0.75% levobupivacaine with 15 ug of epinephrine was given. If there was no evidence of intravascular or subarachnoid injection, the remaining amount of study drug was administered over 5 minutes to a maximum of 20 ml according to the following schemata:

1. Administer test dose and wait 2 minutes
2. Administer 6 ml of levobupivacaine and wait 1 minute
3. Administer 6 ml of levobupivacaine and wait 1 minute
4. Administer 5 ml of levobupivacaine

After the injection of the anesthetic and placement of the epidural catheter, sensory block was assessed at 0, 2, 5, 10, 15, 20, 25, and 30 minutes or until an appropriate block for surgery (T10-L4) had been achieved. Immediately after the injection, all patients were started on their randomized study drug infusion (Time 0) at 4 ml/hr via the epidural catheter. The infusion either contained 0.125% levobupivacaine combined with fentanyl (4ug/ml), 0.125% levobupivacaine alone or fentanyl (4ug/ml) alone.

Additional doses of midazolam (1-10mg) and propofol were used intra-operatively for sedation, at the discretion of the investigator. However, no non-study analgesics, including local anesthetics, opioids, etc., were to be administered during the infusion period.

After leaving the operating room, the patient self-administered the study drug via patient-controlled epidural anesthesia (PCEA) for a period of 24 hours. If the initial infusion proved to be inadequate, the patient could self-administer 2 ml every 10 minutes to a maximum of 14 ml/hour. If analgesia remained inadequate, the patient received a loading dose of 5 ml of study medication and a nurse increased the infusion rate to 6 ml/hr. If after 30 minutes, the patient still complained of pain, another loading dose of 5 ml of study medication was given and the infusion rate was increased to 8ml/hr.

Thereafter, if the additional medication proved to be insufficient, the anesthesiologist was called. If a femoral nerve block was required for pain relief prior to completion of the 24-hour post-operative period, the patient was discontinued from the study.

Efficacy and safety measurements were made at various time points throughout the surgery and 24-hour post-operative period, unless the patient was asleep, stable and/or comfortable.

Table 104. Schedule of Assessments

Table 1 Schedule of Assessments

Study Parameter	Pre-Study	Pre-Surgery	Surgery	Post-Surgery
History and Patient Consent	X			
Physical Exam[1]	X			
12-lead ECG	X			
Vital Signs	X		Every 30 minutes	Time 6, 12, 18 and 24 hours
Epidural Anesthesia		X		
Study Medication		X	X	Via PCEA[2]
Sensory Block		0, 2, 5, 10, 15, 20, 25, 30 minutes or every 30 minutes until adequate block is achieved, T10-L4		Time 6, 12, 18, and 24 hours
Motor Block (modified Bromage scale)[3]		0, 10, 20, and 30 minutes or until a score of 3 is achieved		In the recovery room, then at 6, 12, 18, and 24 hours
Cardiovascular Monitoring, continuous			X	
VAS Pain Rating[4]				Time 6, 12, 18, and 24 hours[5]
Overall Assessment of Sensory and Motor Block				X
Clinical Laboratory Sampling	X			X
Adverse Events	X	X	X	X[6]

[1]Includes body weight and height. [2]Patient self medication of analgesia. Should the analgesia not be sufficient the patient may receive up to two loading doses with an increase in the infusion rate of study medication, before the anesthesiologist is contacted for a femoral block. [3]Was assessed on the unaffected limb. [4]Assessments were made at rest and upon movement. [5]Global VAS rating of overall pain was assessed by the patient and the anesthesiologist at the end of the study. [6]Within 3-7 days post-discharge to determine residual effects of the study drug.

[Sponsor's Table 1, "Schedule of Assessments", Item 8, Vol. 1.75 p.031]

The primary efficacy endpoint was the time to first request for administration of PCEA in the 24 hour post-operative period. The secondary endpoints were: (1) to assess the volume of rescue analgesia required in the 24-hour post-operative period; (2) to assess motor block and pain (VAS) at various time points; (3) to evaluate the relative safety and efficacy profiles of the three different treatment groups

Sensory block was assessed at 0, 2, 5, 10, 15, 20, 25, and 30, minutes or until an appropriate block (T10-L4) for orthopedic surgery was achieved. After surgery, sensory block was assessed at 6, 12, 18, 20 and 24 hours from Time 0.

Motor block assessments were made using the modified Bromage scale at Time 0, and 10, 20, and 30 minutes (or until a score of 3 had been achieved). Thereafter, assessments were made at 6, 12, 18 and 24 hours from Time 0.

The Visual Analog scale (VAS) was assessed at rest and upon movement at 6, 12, 18 and 24 hours from Time 0. A global VAS rating for overall pain satisfaction was completed at study end by both the patient and investigator.

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 patient who received either the pre-surgical 0.75% levobupivacaine or the randomized study drug were included in the safety population. Patients who received 0.75% levobupivacaine during surgery but who did not receive the post-surgery study drug were included in all safety analyses as a fourth treatment group.

The following strata were used to define the center and type of surgery combined. No summary statistics were made for center or type of surgery alone.

Site 01 – Hip Patients
Site 01 – Knee Patients
Site 02 – Hip Patients

"All efficacy analyses were done on the Intent-to-Treat population. The key comparison was between the fentanyl and levobupivacaine plus fentanyl 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/type effect was adjusted for all analyses."

[Item 8. Vol. 1.75, p.035-037]

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 by PCEA. The center/type of surgery was used as a stratification factor in the model. Pairwise comparisons were generated by analyzing only two treatment groups. The ITT population was used. A supportive survival analysis, utilizing the per-protocol population, is presented."

[Item 8, Vol. 1.72, pp. 037]

Secondary Efficacy Analyses

"The volume of rescue medication administered by PCEA, motor block at four time points, and VAS at rest or following movement at four time points was analyzed by a two-way ANOVA with treatment, strata, and their interaction as the independent variables at each time point. SAS Type III estimable functions were used. The confidence interval (CI) of the pairwise difference of the means was based on the adjusted means from this model. If appropriate, a transformation (e.g., arcsine), logistic regression, or non-parametric statistics were used. The dichotomous parameters, proportion of patients who requested rescue medication and usage of femoral nerve block, were analyzed by a Cochran-Mantel-Haenszel test controlling for strata. The CI 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."

Other Parameters

"Descriptive statistics for the time to onset of sensory block adequate for surgery and maximum spread of pre-surgery sensory block are presented."

"Time to onset of sensory block adequate for surgery was 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, time to onset was defined as the start time of surgery."

"Maximum spread of 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. 037 - 038]

ıanges to the Planned Statistical Methods

"Several changes and clarifications to the planned statistical methods were made. The following modifications to tables were made on August 21, 1997, prior to the unblinding of the study.

- Descriptive statistics for total volume of 0.75% levobupivacaine for surgery are presented. A new table was added to present the amount of study drug infusion per hour on study.

- Sensory block was defined as T10 or above. The proportion of patients with adequate sensory block is presented instead of time to onset of adequate sensory block.

- The table presenting the number of patients experiencing 30% fall in systolic blood pressure was subset into three tables: (1) from the start of study drug administration to or at surgery time, (2) during surgery, and (3) after surgery to end of infusion

- All adverse events with onset date/time after study drug administration are tabulated, including any adverse events with missing onset time on the date of study drug administration and any at least unlikely drug-related adverse events with missing onset date. Pre-treatment adverse events are excluded from the tabulations.

The vasopressor medication data listing is not provided.

- After the data were unblinded, it was observed that in certain analyses (e.g., overall assessment of pain) one of the cells in the two-way ANOVA model had zero observations (i.e., Site 01 knee fentanyl patients). In order to test the model, the data from this strata (Site 01 knee patients) was dropped. The overall comparison was then on the hip patients from the two centers."

[Item 8, Vol. 1.72 , p. 039]

PROTOCOL AMENDMENT:

This amendment was dated 4/29/97. It consists of the following changes:

A. Study Design
- Time and indication for the 20-gauge end-hole catheter has been included, as follows: "During surgery and for post-operative analgesia, study drug infusion will be via 20-gauge end-hole catheter."

B. Regional Anesthesia
- Editorial changes.

C. Follow-up
- A more complete statement of the follow-up procedure including examples of the open-ended questions to be used.

D. Adverse Event Reporting
- Editorial changes which delete examples of the adverse events to be reported.

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 levobupivacaine/fentanyl group, 23 in the levobupivacaine group and 23 in the fentanyl group. Of the 68 patients randomized, 66 (97.0 %) received study medication and were considered to be included in the safety population.

Two patients (No. 005-01 randomized to levobupivacaine and No. 017-01 randomized to the combination) discontinued prior to receiving 0.75% levobupivacaine as pre-operative anesthesia. The remaining 66 patients were considered evaluable for safety.

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. Patient # 002-01 (randomized to the combination) received 0.75% levobupivacaine as pre-surgical anesthesia but experienced an intravascular injection and was withdrawn prior to receiving the study drug. The remaining 65 patients received randomized study drug and were included in the ITT population.

The per-protocol population was defined as those patients who received study drug and were not technical failures or major protocol violators. Four patients (Nos. 006 - 01, 068-01, 072-01 randomized to the combination and 066-01 randomized to levobupivacaine) were considered technical failures and one patient (No. 070-01 randomized to levobupivacaine) was classified as a protocol violator. Thus, of the 65 patients who received their randomized study analgesic, five were excluded from the per-protocol population.

Twenty-eight patients discontinued before the end of the 24-hour post-operative study period and 40 patients completed the study.

Table 105. 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**
005/01	Levobupivacaine (Not Treated)	Patient Withdrew	
017/01	Fentanyl (Not Treated)	Spinal Tap	
Excluded from Intent-to-Treat:			**65(95.6) Intent-to-Treat**
002/01	Combination	Intravascular Injection of Study Drug	
Excluded from Per-Protocol:			**60 (88.2) Per-Protocol**
006, 068 and 072/01;	Combination	Technical Failure	
066/01	Levobupivacaine		
070[9]/01	Levobupivacaine	Femoral Nerve Block Required Prior to End of 24-hour Infusion	
Other Withdrawals:			
076/01	Combination	Femoral Nerve Block Required Prior to End of 24-hour Infusion	
007,063,064/01	Levobupivacaine		
069, 075,077,080/01	Fentanyl		
001,012,016,067/01	Levobupivacaine	Unable to Control Post-Operative Pain	
003, 061/01	Fentanyl		
203,214/02	Levobupivacaine	Patient Exhausted Drug Supply	
010[10]/01	Fentanyl	Surgeon Gave Patient Bupivacaine	
201/01	Fentanyl	SAE – Shortening of Leg Following Hip Replacement	
215/02	Fentanyl	Patient Request[11]	
211/02	Fentanyl	Patient Inadvertently Taken Off of Study Drug Prior to End of 24-hr Infusion	
28 (41.2 %) Total Withdrawals			**40 (58.8%) Total Completed**

[9] Not clear why Patient 070/010 was eliminated from the per-protocol group when others with the same protocol violation were not eliminated.

[10] In response to FDA questions, the sponsor submitted a table (11/5/98) outlining the patient withdrawals from CS-006. It was found to contradict the text found in Item 8, Vol. 1.75 p. 040 –"10.1. Patient Disposition"

[11] 6/19/97 - Following Hip Replacement - PCA contained Bupivacaine and Fentanyl

Table 106. Patient Disposition

Table 2 Patient Disposition

Patients	Levobupivacaine/ Fentanyl N (%)	Levobupivacaine N (%)	Fentanyl N (%)	All Patients N (%)
Patients Randomized	22 (100)	23 (100)	23 (100)	68 (100)
Withdrawn Prior to Anesthesia (Not Treated)	0	1 (4.3)	1 (4.3)	2 (2.9)
Received Levobupivacaine for Anesthesia (Safety Population)	22 (100)	22 (95.7)	22 (95.7)	66 (97.1)
Received Randomized Study Drug (ITT Population) for Analgesia	21 (95.5)	22 (95.7)	22 (95.7)	65 (95.6)
Per-Protocol Evaluable	18 (81.8)	21 (91.3)	21 (91.3)	60 (88.2)
Non-Protocol Evaluable	3 (13.6)	1 (4.3)	1 (4.3)	5 (7.4)
Discontinued	5 (22.7)	11 (47.8)	12 (52.2)	28 (41.2)
Completed	17 (77.3)	12 (52.2)	11 (47.8)	40 (58.8)

Abstracted from Statistical Table 1.

[Sponsor's Table 3., Item 8, Vol. 1. 75, p. 041]

Demographics

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

Table 107. Demographics - Intent-to-Treat Population

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

Variable	Levobupivacaine/ Fentanyl	Levobupivacaine	Fentanyl	All Patients
Sex N (%)				
Male	9 (42.9)	7 (31.8)	4 (18.2)	20 (30.3)
Female	12 (57.1)	15 (68.2)	18 (81.8)	45 (69.2)
Race N (%)				
Caucasian	20 (95.2)	20 (90.9)	22 (100)	62 (95.4)
Black	1 (4.8)	0	0	1 (1.5)
Hispanic	0	2 (9.1)	0	2 (3.1)
Age (years)				
Mean ± S.D.	62.3 ± 12.97	69.7 ± 8.95	66.7 ± 8.3	66.3 ± 10.67
Median	66.0	72.0	69.0	69.0
Minimum	24	42	44	24
Maximum	76	80	79	80
Weight (kg)				
Mean ± S.D.	81.71 ± 14.67	78.37 ± 12.75	83.93 ± 14.19	81.33 ± 13.86
Median	85.50	77.0	82.15	80.30
Minimum	52.0	50.9	56.0	50.9
Maximum	106.7	106.5	110.0	110.0

Abstracted from Statistical Table 3.2.

[Sponsor's Table 3., Item 8, Vol.1.75, p. 042]

More women (69.2%) than men (30.3%) were enrolled in this study. The majority of patients were Caucasian (95.4%), with a mean age of 66.3 years and weight of 81.3 kilograms.

Upon review of the "Data Listings" the overall medical histories at screening, covered a broad range of conditions. Virtually every organ systems was represented including the following: cardiovascular, genitourinary, rheumatologic, endocrine, musculoskeletal, pulmonary, etc.

Concomitant medications most commonly administered included pre-operative sedatives, nausea prophylaxis, anesthetics and anesthetic reversal agents, vasopressors and pain medications.

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Variables:

The primary measure of efficacy was the time to first verbal request for administration of PCEA in the first 24 hours post-operatively. The key comparison is the combination versus fentanyl alone.

"The levobupivacaine/fentanyl combination was statistically superior to fentanyl (p=0.007) and to levobupivacaine (p=0.006). The median time to analgesic request in the levobupivacaine/fentanyl combination group was 8.9 hours compared with 7.5 hours in the levobupivacaine group and 6.9 hours in the fentanyl group."

The statistical reviewer disagreed with the number of censored observations used in the sponsor's analysis of this endpoint. However, the amount of bias introduced was too small to change the p-value significantly.

[Item 8. Vol. 1.75, p. 043]

Table 108. Time (Minutes) to First Request for Rescue Analgesia

Table 4 Time (Minutes) to First Request for Rescue Analgesia: Intent-to-Treat Population

Time to first request for rescue analgesia (min)	Levobupivacaine/ Fentanyl	Levobupivacaine	Fentanyl
Percentile			
25%	433.0	359.0	341.0
50%	535.0	448.0	416.0
75%	1000.0	495.0	479.0
Number of censored observations	5	1	1
Mean[1,2]	603.05	421.50	420.45

[1] Arithmetic Mean. [2] If additional dose was not requested during the 24-hour period, the time of the first request for rescue medication was censored at the completion time of the study drug administration in the 24-hour post-operative period. Means calculated using censored data are negatively biased. Due to differential group censoring, the combination group has the greatest negative bias and the levobupivacaine treatment has the least negative bias.

Pairwise Comparisons:	p - value
Combination versus fentanyl	0.007
Levobupivacaine versus fentanyl	0.679
Combination versus levobupivacaine	0.006

Abstracted from Statistical Table 7.1.

[Sponsor's Table 4, Item 8, Vol. 1.725 p. 043]

Secondary Efficacy Variables:

Secondary efficacy results included:

1. proportion of patients who did or did not request rescue analgesia,
2. amount of rescue medication administered,
3. proportion of patients who required femoral nerve block,
4. the extent of motor block over time,
5. pain (VAS) at rest and when the patient coughed, and
6. overall pain assessment by patients and investigator at the end of the 24-hour postoperative study period.

Proportion of Patients Who Did or Did Not Request Rescue Analgesia

"Two of the 21 patients (9.5%) in the levobupivacaine/fentanyl combination group did not self administer rescue analgesia during the 24-hour post-operative study period compared with one of 22 patients (4.5 %) in the levobupivacaine group and none in the fentanyl group."

"Four patients had missing data: three patients (two in the combination group and one in the fentanyl group) because they received a femoral nerve block prior to the end of the 24-hour post-operative study period, and one (combination group) had an inadequate block. Pairwise comparisons of the number of patients who administered or did not administer rescue medication in the first 24 hours after surgery were not statistically significant across any of the three pairs."

The statistical reviewer has placed this analysis as supportive evidence for the primary efficacy variable and found the results to be similar.

Amount of Rescue Medication Administered

"The amount of rescue medication by volume was compared across treatment groups at 6, 12, 18, and 24 hours. There were no significant differences at any time point, although at 12 hours, a pairwise comparison of the levobupivacaine and fentanyl combination versus fentanyl approached significance ($p = 0.063$). The adjusted mean volume of rescue medication was highest in the fentanyl group and lowest in the combination group."

[Item 8. Vol. 1.75, p. 043- 046]

Table 109. Proportion of Patients Requesting Rescue Analgesia

Table 5 Proportion of Patients Who Self Administered Rescue Analgesia: Intent-to-Treat Population

	Levobupivacaine/ Fentanyl N =21 n (%)	Levobupivacaine N = 21 n (%)	Fentanyl N = 21 n (%)
Patients who self administered rescue medication	16 (76.2)	21 (95.5)	21 (95.5)
Patients who did not self administer rescue medication)	2 (9.5)	1 (4.5)	0
Missing Data	3 (14.3)	0	1 (4.5)

Pairwise Comparisons	p - value
Combination versus fentanyl	0.126
Levobupivacaine versus fentanyl	0.386
Combination vers is levobupivacaine	0.355

Abstracted from Statistical Table 7.3.

Table 110. Amount of Rescue Analgesia Administered Post-Operatively

Table 6 Amount of Rescue Study Medication Administered Over 24 Hours: Intent-to-Treat Population

Amount of Study Drug (mL) in 24 Hours	Levobupivacaine/ Fentanyl N = 21	Levobupivacaine N = 22	Fentanyl N = 22
Adjusted mean ± S.D.	118.40 ± 63.25	131.80 ± 74.16	129.41 ± 59.87
Arithmetic mean	118.40	134.65	129.17
Median	116.00	118.00	138.40
Minimum	1.5	16.3	2.0
Maximum	272.0	250.0	219.8

Pairwise Comparisons	Mean Difference (95% Confidence Interval)	p - value
Combination versus fentanyl	-49.58, 27.57	0.570
Levobupivacaine versus fentanyl	-35.91, 40.69	0.901
Combination versus levobupivacaine	-52.10, 25.31	0.491

Abstracted from Statistical Table 7.5.

[Sponsor's Table 5 and 6. Item 8, Vol. 1.72, p.045]

Proportion of Patients Requiring Femoral Nerve Block

"Twelve patients, all undergoing knee surgery, required femoral nerve block prior to the end of the 24-hour post-operative study period. There was a similar incidence across treatment groups." No statistically significant differences were found.

[Item 8, Vol. 1.75, p. 046]

Table 111. Patients Requiring Femoral Nerve Block

Table 7 Patients Requiring Femoral Nerve Block for Pain Control Within 24 Hours: Intent-to-Treat Population

	Levobupivacaine/ Fentanyl N =21 n (%)	Levobupivacaine N = 21 n (%)	Fentanyl N = 21 n (%)
Patients who required femoral nerve block	3 (14.3)	4 (18.2)	5 (22.7)
Patients who did not require femoral nerve block	17 (81.0)	18 (81.8)	17 (77.3)
Missing Data	1 (4.8)	0	0

Pairwise Comparisons	p - value
Combination versus fentanyl	0.298
Levobupivacaine versus fentanyl	0.414
Combination versus levobupivacaine	0.789

Abstracted from Statistical Table 8.

[Sponsor's Table 7, Item 8, Vol. 1.75, p. 046]

xtent of Motor Block Over Time

"The extent of post-surgery motor block was assessed at 6, 12, 18, and 24 hours post-operatively or until the patient has no lingering paralysis. At six hours post surgery the patients in the levobupivacaine/fentanyl combination group had slightly more remaining paralysis (p =0.085). By 12 hours post surgery most patients had regained full movement of their lower limbs."

Table 112. Analysis of Secondary Efficacy Variable

TABLE 9

POST SURGERY MOTOR BLOCK GRADE OVER TIME

INTENT-TO-TREAT PATIENTS

TIME		0.125% LEVOBUPIVACAINE AND FENTANYL	0.125% LEVOBUPIVACAINE ALONE	FENTANYL ALONE	MEAN DIFFERENCE (95% CI) (2)	P-VALUE (2)
OVERALL						
PROPORTION OF PATIENTS REACHING GRADE (1)						
6 HOURS	MISSING	3 (14.3%)	4 (18.2%)	3 (13.6%)		0.813
	0	9 (42.9%)	9 (40.9%)	16 (72.7%)		
	1	6 (28.6%)	2 (9.1%)	2 (9.1%)		
	2	2 (9.5%)	3 (13.6%)	1 (4.5%)		
	3	1 (4.8%)	4 (18.2%)	0		
	N	18	18	19		
	ADJUSTED MEAN	0.7	1.1	0.2		
	ARITHMETIC MEAN	0.7	1.1	0.2		
	MEDIAN	0.5	0.5	0.0		
	STD. DEV.	0.89	1.28	0.54		
PAIRWISE COMPARISONS						
	COMBINATION VS. FENTANYL				0.5 (-0.1, 1.1)	0.085
	LEVOBUPIVACAINE VS. FENTANYL				0.9 (0.3, 1.5)	0.004
	COMBINATION VS. LEVOBUPIVACAINE				-0.4 (-1.0, 0.2)	0.199

(1) Bromage Scale: 0=no paralysis, full flexion of knees and ankles; 1=inability to raise extended leg, able to move knees; 2=inability to flex knees, able to flex ankles; 3=inability to move lower limbs.

(2) P-value and adjusted mean from analysis of variance with factors of treatment, strata, and their interaction. The 95% confidence interval is based on adjusted means of the pairwise differences from this model. Due to zero observations in the site 01-knee fentanyl group, all knee patients were removed from this model at 18 and 24 hours.

PROJECT16:[CDIRC0907.TABLES]T09.SAS 12:04 September 15, 1997 Reference: LISTING 10.2

[Sponsor's Table 9, item 8, Vol. 1.75, p. 442]

ain (VAS) at Rest and When the Patient Coughed

"The post-surgery Visual Analog Scale (VAS) assessments were obtained 6, 12, 18, and 24 hours post-operatively both at rest and following movement. At the six and 12 hour time points at rest, patients in the combination group rated their discomfort as significantly less than the fentanyl group (p= 0.022 and 0.002, respectively). Similarly, VAS scores following movement at six and 12 hours post-surgery were significantly lower for patients in the combination group than for patients in the fentanyl group (p = 0.036 and 0.001, respectively). At the 18 and 24 hour time points, at rest or following movement, there was no difference in VAS scores between the treatment groups." See Sponsor's Table10.1 and 10.2 Appendix 8, Item 8, Vol. 1.76, p. 001-032]

Overall Pain Assessment by Patients and Investigator at the End of the 24-hour Post-Operative Study Period

"At the end of the study, both patients and the investigators gave an overall assessment of pain. For the assessments included (patients in the knee surgery strata were excluded due to missing data), the overall patient assessment means were 1.66, 2.81, and 3.82 on the VAS scale for the combination, levobupivacaine, and fentanyl groups, respectively. The 2.16 point difference between the combination versus fentanyl groups was statistically significant (p = 0.007). The combination group patients (adjusted mean = 1.35) had significantly lower (p = 0.005) overall investigator pain assessment scores than the fentanyl group patients (adjusted mean = 54)."

[Item 8. Vol. 1.75 p. 046 – 047]

REVIEWER'S EFFICACY DISCUSSION

The primary measure of efficacy, the time to first request for administration of PCEA in the 24-hour post-operative period following surgery, was significantly longer in the levobupivacaine/fentanyl combination treatment group compared to the fentanyl treatment group (p=0.007). This statistical difference was also demonstrated in the analysis of the secondary efficacy variables – VAS and global assessments – where pain was less at the 6 hour (p =0.022) and 12 hour (p =0.002) post-operative time points in patients in the combination treatment group.

There was no difference, however, in the amount of rescue medication used over the 24-hour study period, or the proportion of patients requiring femoral nerve block across the treatment groups.

The sponsor has separated patients according to the following categories:
(1) "femoral nerve block required prior to the end of the 24-hour infusion" (9/68, 13.2%)
(2) "unable to control post-operative pain"(6/68; 8.8%)
(3) "patient exhausted supply of study drug" (2/68; 2.9%)
(4) "patient noticed a difference in analgesia from previous PCA mixture containing bupivacaine/fentanyl, (1/68; 1.5%),

However, it is not unreasonable to assume that, in fact, all of these categories represent inadequate pain relief. Accordingly, if one were to group these patients into one category of patients with inadequate pain relief, it becomes clear that there was a significant number of patients complaining of inadequate pain relief, i.e., 18/68 '26.4%). The clear majority (19/20; 95%) of this subset of patients were those in the single therapy treatment ms.

When analyzing the data from this prospective, it begs the question - why were so many patients inadequately controlled with single therapy infusion of levobupivacaine when a previous study (Study # 030475) demonstrated levobupivacaine effective in managing post-operative orthopedic surgery pain? Is the answer found in the dosages used in the two studies or were these above mentioned patients not in the levobupivacaine single therapy infusion group?

The answer to these questions does not, unfortunately, clear up the discrepancy. The dosages in the two studies were the same, i.e., 0.125% levobupivacaine in Study # CS 006 and 0.0625 – 0.25% levobupivacaine in Study 030475. In Study CS 006, there were just as many patients in the fentanyl alone group as there were in the levobupivacaine alone group who required extra measures to control their pain.

Upon discussion with the statistical reviewer, the Intent-to-Treat population included above-mentioned group of patients; therefore, the primary analysis was not affected.

Despite the uncertainty of the effectiveness of levobupivacaine when used alone to control post-orthopedic surgery pain, it has demonstrated to be effective when used in combination with fentanyl in this setting.

STUDY # 030742

PROTOCOL SYNOPSIS:

Title: "A Study to Assess the Efficacy and Safety of 0.125% Levobupivacaine, 0.125% Levobupivacaine Plus 50ug/h Clonidine and 50ug/h Clonidine Alone Administered as a Continuous Extradural Infusion for Post-operative Pain in Patients Undergoing Elective Hip Replacement Surgery."

Primary Objective: "To compare the analgesic efficacy of levobupivacaine alone, clonidine alone and levobupivacaine plus clonidine after surgery"

Secondary Objective: "To evaluate the safety of each of the formulations used in the study."

[Item 8, Vol. 1.78, p. 022]

nsory block was assessed using a response to ice immediately before the initial study drug administration, and at 5-minute intervals up to 30 minutes after completion of the epidural injection. Additionally, assessments were made hourly up to 24 hours after the infusion commenced. Sensory block reassessments occurred in the event of an inadequate block at 5-minute intervals until the block was adequate for surgery to proceed or the patient was withdrawn.

Motor block assessments were made using the modified Bromage scale at Time 0, and hourly up to 24-hours after commencement of the epidural infusion.

The Visual Analog scale (VAS) was assessed until 12 hours post commencement of the epidural infusion, 2 hourly thereafter up to 24 hours provided the patient was awake. Recordings were taken for pain at rest and on passive flexion of the operated limb.

Efficacy Measurements

The primary efficacy endpoint was the total dose of morphine delivered via the PCA pump during the 24-hour post-operative infusion period.

The secondary endpoints were:

(1) time to first request for analgesia during the 24 hour period following completion of the epidural injection and
(2) number of requests for analgesia.

STATISTICAL ANALYSIS

The Intent-to-Treat population was defined as all randomized patients who received the complete 24 hour infusion of study medication. The analysis of efficacy data was performed on the Intent-to-Treat population with confirmatory analysis on the per-protocol population. The per-protocol population was determined after all protocol violations and deviations were identified and prior to breaking the study blinding.

"The primary measure of efficacy was defined to be the total dose of morphine delivered via the PCA pump during the 24-h post operative infusion. The statistical hypothesis behind this trial was as follows:

H_0: the mean difference in the dose of morphine delivered in patients receiving an infusion between the treatment groups (0.125% levobupivacaine, 0.125% levobupivacaine plus 50 ug/h clonidine and 50 ug/h clonidine) is equal to zero.

H_1: the mean difference in the dose of morphine delivered in patients receiving an infusion between the treatment groups (0.125% levobupivacaine, 0.125% levobupivacaine plus 50 ug/h clonidine and 50 ug/h clonidine) is not equal to zero."

"The total dose of morphine was initially analysed using analysis of variance (ANOVA) with the term for treatment. The residuals from the analysis were submitted to a Shapiro-Wilk test for normality and examined graphically to assess variance homogenicity. Since the residuals deviated from the assumptions a re-analysis of the data was required. Since zero values were present a log transformation of the data was inappropriate and hence a non-parametric method was required, namely the wilcoxon two-sample test. To compensate for multiple comparisons, a sequentially rejective Bonferroni-Holm method was to be used (ie in order to attain an overall 5% significance level, the greatest difference between treatments was required to attain significance at 1.7%, the second greatest difference at the 2.5% level and the smallest difference at the 5% level). The estimate of treatment difference and associated 95% confidence intervals were based on Wilcoxon's two-sample test."

"The mean, standard deviation, median, minimum and maximum morphine requirements were tabulated by treatment group."

[Item 8. Vol. 1.78, p. 039 - 040]

Time to First Request for Morphine via the PCA Pump

The time to first request for morphine *via* the PCA pump was intended to be analysed using analysis of variance techniques similar to those intended for the primary efficacy variable. Since this was deemed inappropriate due to the non-normality of the data, non-parametric techniques were employed, namely the Wilcoxon two-sample test. As the time to first request for analgesia included censored observations (ie some patients did not request relief analgesia during the 24 h post surgery) a secondary analysis using survival analysis techniques has been performed. It should be noted that censored observations (set at 24 h for first request since infusion period was of this time scale) were included in this analysis."

As part of the survival analysis, the proportion of patients requesting relief analgesia has been illustrated using Kaplan-Meier survival curves. Furthermore, plots of the negative log of estimated survival function against time and the log of the negative log of the estimated survival function against time were made. Since proportionality was not encountered in the latter plot for any of the pairwise comparisons, Cox's regression was deemed inappropriate and hence the Wilcoxon test was used."

"Because of the similarity of the tests used in order to analyse the data, it was deemed that the Wilcoxon result produced by survival analysis techniques was more appropriate due to the type of data and the inclusion of censored observations. For this reason, no non-parametric results have been presented."

"The median, 25th, 75th and 90th percentile for the time to relief analgesia have been presented for each treatment group (both including and excluding censored observations). The number of censored observations (i.e., no relief analgesia administered prior to end of extradural infusion) has also been shown."

[Item 8, Vol. 1.78, p. 040-041]

Number of Requests for Analgesia via the PCA Pump

The number of requests for analgesia via the PCA pump were intended to be analysed using identical methods as the primary efficacy variable (i.e., ANOVA). Since the residuals did not satisfy the assumptions required non-parametric techniques were employed, namely the Wilcoxon two-sample test."

"The mean, standard deviation, median, minimum and maximum number of requests for analgesia have been tabulated by treatment group."

Visual Analogue Pain Scale

"The visual analogue pain scores were recorded hourly until 12 h post commencement of extradural infusion (provided surgery was over) and two hourly thereafter up to 24 h provided the patient was awake using a 10 cm visual analogue scale from 0-10 where '0 = no pain' and '10 = worst imaginable pain'."

"The visual analogue pain scores recorded at rest and on passive movement both included 2 summaries. The first summary was of all assessments regardless of when rescue analgesia was requested, the second was of the scores recorded up to the request for rescue analgesia."

Height of Sensory Block

"Sensory block was assessed hourly (provided surgery was over), up to 24 h if patients were awake, unless the block had disappeared. Sensory block was assessed using response to ice."

In order to summarise the height of block, scores were assigned to the upper and lower dermatomes as follows: scores 1, 2, 3 8 to dermatomes C1, C2, C3 C8; scores 9,10,..., 20 to dermatomes Th1 to Th12 (sometimes written as T1 to T12); scores 21, 22,..., 25 to L1 to L5 and scores 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 have been 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 log it model with a term for treatment. Pairwise comparisons between treatment groups have been 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 has been used in order to test the proportional odds assumption.

[Item 8. Vol. 1.78, p. 042-044]

PROTOCOL AMENDMENT:

This amendment was dated 6/10/1997. It consists of the following changes:

A. Post-operative Period

- Sensory and motor block assessments were made on an hourly basis up to 24 hours after the start of the infusion. VAS pain scores, however, were completed hourly until 12 hours after the start of the infusion and two hourly, thereafter, up to 24 hours.
- A sentence has been added which clarifies concomitant medication violations. It is as follows: "If patients receive any analgesia including NSAIDS and prophylactic analgesics prior to the first dose of intravenous morphine the patient will be deemed non-evaluable and will only be followed for safety data."

B. Administrative Changes

- Recorded information includes, vital signs, continuously intra-operatively and up to 27 hours post-injection, intravenous fluid intake, adverse events, medications used, etc.

C. Follow-Up

- Statement of the follow-up procedures including examples of open-ended questions to be asked post-operatively.

CONDUCT OF STUDY

Patient Distribution/Disposition:

A total of 98 patients were randomized into three treatment groups: 31 (31.6%) of patients in the levobupivacaine group, 32 (32.7%) in the levobupivacaine/clonidine group and 35 (35.7%) in the clonidine group. Of the 98 patients randomized, 96 (98%) received study medication and were considered to be included in the safety population.

Two patients (No. 18A randomized to levobupivacaine and No. 20A randomized to clonidine) were discontinued prior to receiving 0.75% levobupivacaine as pre-operative anesthesia, the reason given was "technical failure". The remaining 66 patients were considered evaluable for safety. Note: Patients whose numbers had been previously assigned, were assigned the letter 'A'.

Five patients (Patient Nos. 010, 013A, 036A, 058 and 069) received 0.75% levobupivacaine as pre-surgical anesthesia but did not receive any infusion and therefore were not eligible for the Intent-to-Treat population. In addition, Patient 042 did not receive a full 24 hours of infusion (patient was confused, aggressive and therefore unable to complete the assessments) and therefore was also excluded from the Intent-to-Treat population. The Intent-to-Treat population included 30 patients (93.8%) in the levobupivacaine/clonidine group, 30 patients (96.8%) levobupivacaine group, and 30 patients (85.7%) from the clonidine group.

Patient 010 randomized to the combination experienced a technical failure and recorded an insufficient block, Patient 013A who was randomized to clonidine awakened at surgery, moving, wheezing and was given a general anesthetic and withdrawn, Patient 036A randomized to clonidine experienced a technical failure, Patient 8 randomized to the combination experienced a technical failure, and Patient 069 randomized to clonidine experienced an insufficient block.

Four patients (Nos. 028,056,093,and 080) were classified as major protocol violators and were excluded from the per-protocol population. Hence the per-protocol population included 27 patients (87.1%) from the levobupivacaine group, 30 patients (93.8%) from the combination group and 29 patients (82.9%) from the clonidine group. Patients 028 received NSAIDS or analgesics during infusion, Patient 056 and 093 received NSAIDS or other analgesics after 10PM on the day before surgery. Patient 080's start time of infusion was less than 2.5 hours after the increment of epidural injection.

Other per-protocol violations that were not considered reasons for withdrawals included:

- Sample for laboratory analysis taken before the completion and removal of epidural infusion - Patient 007 (levobupivacaine), Patient 008 (combination), Patient 060 (clonidine)
- Invalid time for injection – Patient 085 (clonidine)
- Incorrect procedure used for extra bolus injections – Patient 031 (levobupivacaine) and Patient 013 and 016 (clonidine)
- No sensory block measured in 5 min intervals after the first 5 ml injection -Patient 031 (levobupivacaine)
- ECG started earlier than 45 min after her last injection – Patient 064 (combination)
- Reaction to the incision at the start of surgery – Patient 016 (clonidine)

Table 113. Patient – Specific Protocol Violations

PATIENT NUMBER/CENTER	TREATMENT GROUP	VIOLATION	PATIENT TOTALS N (%)
			98 (100) Randomized
Excluded from Safety Population:			**96(97.9) Safety Population**
018A	Levobupivacaine (Not Treated)	Insufficient Block	
020A	Clonidine (Not Treated)		
Excluded from Intent-to-Treat:		Did Not Received Full 24 hour Infusion	**90 (91.8) Intent-to-Treat**
010,058	Combination		
013A, 042, 036A, 069	Clonidine		
Excluded from Per-Protocol:			**86 (87.5) Per-Protocol**
028, 056	Levobupivacaine	Received Unauthorized NSAIDS	
093	Clonidine		
080	Levobupivacaine	Unauthorized Infusion Start Time	
Other Violations:			
008	Combination	Sample for laboratory analysis taken before the completion and removal of epidural infusion	
007	Levobupivacaine		
060	Clonidine		
085	Clonidine	Invalid time for injection	
031	Levobupivacaine	Incorrect procedure used for extra bolus injections	
013, 016	Clonidine		
031	Levobupivacaine	No sensory block measured in 5 min intervals after the first 5 ml injection	
064	Combination	ECG started earlier than 45 min after her last injection	
016	Clonidine	Reaction to the incision at the start of surgery	
8 (8.2 %) Total Withdrawals			**90 (91.8%) Total Completed**

Table 114. Population Disposition

Summary of formation of populations

by treatment group

Total population

Evaluation group	Levobupivacaine (n=31)	Levobupivacaine plus Clonidine (n=32)	Clonidine (n=35)
Total population	31 (100.0%)	32 (100.0%)	35 (100.0%)
Safety population	30 (96.8%)	32 (100.0%)	34 (97.1%)
Intent-to-treat population	30 (96.8%)	30 (93.8%)	30 (85.7%)
Per-protocol population	27 (87.1%)	30 (93.8%)	29 (82.9%)

[Sponsor's Table 6., Item 8, Vol. 1. 78, p. 076]

The most common reason for withdrawal was technical failure. 20 patients were found to have 11 types of protocol violations. In addition to these violations, 4 patients were classified as major protocol violators and were excluded from the per-protocol population.

Demographics

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

Table 115. Demographics - Intent-to-Treat Population

TABLE 7

LEVOBUPIVACAINE - 030742

Demographic details

by treatment group

Intent-to-treat population

Variable		Levobupivacaine (n=30)	Levobupivacaine plus Clonidine (n=30)	Clonidine (n=30)
Sex	male	13 (43.3%)	6 (20.0%)	13 (43.3%)
	female	17 (56.7%)	24 (80.0%)	17 (56.7%)
Age (years)	mean	64.9	64.6	67.2
	sd	9.9	9.4	7.8
	minimum	40	45	51
	maximum	78	80	80
	n	30	30	30
Race	white	30 (100.0%)	30 (100.0%)	30 (100.0%)
	black	0 (0.0%)	0 (0.0%)	0 (0.0%)
	hispanic	0 (0.0%)	0 (0.0%)	0 (0.0%)
	asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
	other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)	mean	164.1	160.4	164.3
	sd	8.1	7.9	8.6
	minimum	152	140	152
	maximum	182	177	183
	n	30	29	29
	missing	0	1	1

TABLE 7 (continued)

LEVOBUPIVACAINE - 030742

Demographic details

by treatment group

Intent-to-treat population

Variable		Levobupivacaine (n=30)	Levobupivacaine plus Clonidine (n=30)	Clonidine (n=30)
Weight (kg)	mean	74.74	73.19	72.72
	sd	11.72	13.47	11.80
	minimum	54.1	50.0	50.0
	maximum	100.0	106.0	92.0
	n	30	30	30

[Sponsor's Table 7, Item 8, Vol.1.78, p. 077-078]

the Intent-to-Treat population, the distribution of males and females was identical in the levobupivacaine and clonidine groups (13 males (43.3%) and 17 females (56.7%)) in each, while in the combination group, there were only 6 males (20%) compared to 24 females (80%). On the average, patients in the clonidine group were older (mean 67.2 years, SD=7.8) compared to the levobupivacaine group (mean of 64.9 years, SD=9.9) and combination group (mean of 64.6 years, SD=9.4).

All patients in the study were Caucasian. In the per-protocol population, the demographic trends were similar to those of the Intent-to-Treat population. For example, the clonidine group were slightly older (mean 66.9 years, SD =7.8) than both levobupivacaine (mean 64.9, SD = 9.0 and the combination group (mean 64.6, SD = 9.4).

All patients in the Intent-to-Treat population reported significant medical histories. Patients in the levobupivacaine group reported 100 significant medical histories (95 of which were still present), 88 were reported by patients in the combination group (83 of which were still present) and 93 were reported by patients in the clonidine group (85 of which were still present).

Patients reported significant medical histories in the circulatory and musculoskeletal systems most reported commonly. All patients recording medical histories under these body systems had a disease still present.

All patients in the Intent-to-Treat population reported taking at least one medication at screening which was stopped prior to dosing. All patients recorded a central nervous system and a local anesthetic concomitant therapy.

Twenty-one patients (70%) in the levobupivacaine group reported 56 therapies at screening that continued after dosing, 21 patients (70%) in the combination group reported 57 therapies and 22 patients (73.3%) in the clonidine group reported 69 therapies. The majority of treatment was for hypertension.

erapies started after dosing were, reportedly, for blood and blood-forming organs and the central nervous ystem, predominantly. The majority of patients in the Intent-to-Treat population also received medication for the respiratory system - (70%) in both the levobupivacaine and the combination groups and 73.3% in the clonidine group.

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Variables:

Total Dose of Morphine Administered

"For the intent-to-treat population, the median total dose of morphine administered was lowest in the levobupivacaine plus clonidine treatment group (7 mg over the 24 h period). Patients in the clonidine treatment group received a median value of 21 mg and those in the levobupivacaine treatment group, 36 mg. Also of note was that all patients in the levobupivacaine treatment group received some dose of analgesia whereas not all patients in the other 2 treatment groups did.

Following pairwise comparisons a statistical difference was detected between the treatment groups. The difference was greatest between the levobupivacaine treatment group and the levobupivacaine plus clonidine treatment group ($p<0.001$). The median estimate of treatment difference obtained, based on wilcoxon's two-sample test was equal to 23 mg ie the levobupivacaine plus clonidine treatment group received 23 mg less morphine than the levobupivacaine group. The corresponding 95% confidence interval was (9 mg, 36 mg)."

"Significant differences were also detected at the 5% level between the levobupivacaine plus clonidine treatment group and the clonidine treatment group as well as between the levobupivacaine treatment group and the clonidine treatment group ($p=0.004$ and $p=0.022$ respectively). The median estimate of treatment difference obtained for the levobupivacaine plus clonidine treatment group and the clonidine treatment group was -12 mg (levobupivacaine plus clonidine treatment group - clonidine treatment group) with corresponding 95% confidence interval of (-18, -3). The median estimate of treatment difference obtained for the levobupivacaine treatment group and the clonidine treatment group was 13 mg (levobupivacaine treatment group -clonidine treatment group) with corresponding 95% confidence interval of (2mg, 26mg)."

[Item 8. Vol. 1.78, p. 054 - 056]

or the per-protocol population, similar values were produced for the treatment groups . The median estimates and 95% confidence intervals were also similar. The median estimate of treatment difference obtained for the levobupivacaine treatment group and levobupivacaine plus clonidine treatment group was 22 mg (levobupivacaine treatment group - levobupivacaine plus clonidine treatment group, p<0.001) with corresponding 95% confidence interval of (7 mg, 35 mg). Likewise for the levobupivacaine plus clonidine treatment group and clonidine treatment group the median estimate was -11 mg (levobupivacaine plus clonidine treatment group - clonidine treatment group, p=0.006) with 95% confidence interval of (-18 mg, -2 mg) and for the levobupivacaine treatment group and the clonidine treatment group the median estimate was 13 mg (levobupivacaine treatment group - clonidine treatment group, p=0.028) with corresponding 95% confidence interval of (2 mg, 26 mg).

Table 116. Analysis of Primary Efficacy Variable

TABLE 14

LEVOBUPIVACAINE - 030742

Summary and analysis of total dose of morphine

by treatment group

Intent-to-treat population

Variable		Levobupivacaine (n=30)	Levobupivacaine plus Clonidine (n=30)	Clonidine (n=30)
Morphine requirements (mg)	mean	36.5	13.9	22.6
	sd	23.7	17.3	12.8
	median	36	7	21
	minimum	4	0	0
	maximum	85	60	45
	n	30	30	30
Statistical assessments				
Wilcoxon two-sample test :		p-value	median estimate of treatment differences	95% C.I.s
Levobupivacaine v Levobupivacaine plus Clonidine		<0.001	23 mg	(9, 36)
Levobupivacaine plus Clonidine v Clonidine		0.004	-12 mg	(-18, -3)
Levobupivacaine v Clonidine		0.022	13 mg	(2, 26)

NB: patients with missing doses of morphine have been assumed to have 0mg administered only when the patient did not request morphine

Pair-wise differences between the treatment groups have been estimated as 'Levobupivacaine - Levobupivacaine plus Clonidine', 'Levobupivacaine plus Clonidine - Clonidine' and 'Levobupivacaine - Clonidine'.

[Sponsor's Table 14. Item 8, Vol. 1.78 p. 095]

nalysis of Secondary Efficacy

Time to First Request for Morphine via the PCA Pump

"For the intent-to-treat population the median time to first request for morphine via the PCA pump for patients in the levobupivacaine treatment group was 2.9 h compared with 12.5 h in the levobupivacaine plus clonidine treatment group and 5.9 h in the clonidine treatment group."

"... all patients in the levobupivacaine treatment group received morphine during the 24 h extradural infusion period. Four patients (13.3%) in the levobupivacaine plus clonidine treatment group and one patient (3.3%) in the clonidine treatment group requested no morphine during the 24 h infusion.

"From the survival analysis performed on the time to first request for morphine via PCA pump the Wilcoxon two-sample test indicated significance at the 5% level ($p<0.001$) for the pairwise comparison of the levobupivacaine treatment group and the levobupivacaine plus clonidine treatment group. Significance at the 5% level was also evident in the pairwise comparisons of the levobupivacaine plus clonidine treatment group and the clonidine treatment group as well as the levobupivacaine treatment group and the clonidine treatment group ($p=0.005$ and $p=0.010$ respectively).

[Item 8. Vol. 1.78, p. 056]

Table 117. Analysis of Secondary Measurement –

TABLE 16.1

LEVOBUPIVACAINE - 030742

Summary of time to first request for analgesia

by treatment group

Intent-to-treat population

Analgesia		Levobupivacaine (n=30)	Levobupivacaine plus Clonidine (n=30)	Clonidine (n=30)
Time (hrs) to first request	mean	4.99	12.99	7.20
	sd	5.62	8.32	5.89
	median	2.9	12.5	5.9
	minimum	0.3	0.4	0.2
	maximum	23.8	24.0	24.0
	n	30	30	30
	missing	0	0	0

NB: Patients not requesting relief medication during the infusion period have been censored at 24 hours, i.e. the end of extradural infusion

[Sponsor's Table 16.1 , Item 8, Vol. 1.78, p. 097]

Number of Requests for Analgesia via PCA Pump

For those patients in the intent-to-treat population the median number of requests for analgesia differed greatly between the treatment groups. A median value of 55 requests was calculated for patients in the levobupivacaine treatment group compared to 9 requests for patients in the levobupivacaine plus clonidine treatment group and 28 requests for the clonidine treatment group."

"The difference was greatest between the levobupivacaine treatment group and the levobupivacaine plus clonidine treatment group which was highly significant at the 5% level ($p<0.001$). The median estimate of treatment difference obtained, based on Wilcoxon's two-sample test was equal to 30 more requests by those on levobupivacaine, and the corresponding 95% confidence interval was (11, 56)."

"The difference between the levobupivacaine plus clonidine treatment group and the clonidine treatment group, also significant at the 5% level ($p=0.012$), had a median estimate for treatment difference of -18 requests (levobupivacaine plus clonidine treatment group - clonidine treatment group) with the corresponding 95% confidence interval of (-27, -1). No significant difference was, however, calculated between the levobupivacaine treatment group and the clonidine treatment group ($p=0.13$). The estimated treatment difference between these 2 treatment groups was 17 requests (levobupivacaine treatment group -clonidine treatment group) for analgesia with corresponding 95% confidence interval of (-4, 40)."

"From these results it appears that the levobupivacaine plus clonidine treatment group is the more efficient treatment with less requests made for analgesia, while levobupivacaine treatment group and clonidine treatment group are not significantly different from one another.

em 8, Vol. 1.78, p.057 –058]

Table 118. Analysis of Secondary Outcome Variable – Number of Request for Analgesia

TABLE 17

LEVOBUPIVACAINE - 030762

Summary and analysis of the number of requests for analgesia

by treatment group

Intent-to-treat population

Variable		Levobupivacaine (n=30)	Levobupivacaine plus Clonidine (n=30)	Clonidine (n=30)
Number of requests for analgesia (PCA) pump	mean	68.0	28.7	45.7
	sd	56.0	41.4	46.1
	median	55	9	28
	minimum	5	0	0
	maximum	185	170	183
	n	30	30	30

Statistical assessments

Wilcoxon two-sample test :	p-value	median estimate of treatment differences	95% C.I.s
Levobupivacaine v Levobupivacaine plus Clonidine	<0.001	30 requests	(11, 56)
Levobupivacaine plus Clonidine v Clonidine	0.012	-18 requests	(-27, -1)
Levobupivacaine v Clonidine	0.13	17 requests	(-4, 40)

NB: The number of requests for analgesia was not completed for patient 29; however 3mg of morphine was administered via the PCA pump and hence it was assumed that 3 requests had been made

Pair-wise differences between the treatment groups have been estimated as 'Levobupivacaine - Levobupivacaine plus Clonidine', 'Levobupivacaine plus Clonidine - Clonidine' and 'Levobupivacaine - Clonidine'.

[Sponsor's Table 17. Item 8, Vol. 1.78, p. 100]

sual Analogue Pain Scale

"...the mean VAS scores recorded by the patients in the 3 treatment groups were quire similar over the 24 h time period. A few notable exceptions from this trend were between the 4 and 6 h assessment period in which the levobupivacaine treatment group recorded slightly higher scores, on average, than the other 2 treatment groups. Figure 3, showing the mean VAS scores recorded on passive movement, indicates a similar pattern for the treatment groups although the scores were slightly more sporadic and were seen to be slightly higher towards the end of the assessment period. Both graphs also highlight a high average score recorded at the 16 h assessment by patients in the clonidine treatment group. This was due to large scores being recorded by patients in the clonidine treatment group at this timepoint."

"...the scores were much lower at most timepoints for all 3 treatment groups. However, the mean score in the clonidine treatment group at the 10 h assessment was much higher than the other 2 groups. This can be attributed to the fact that only one patient (Patient 063) had a value recorded on the VAS scale (20 mm). The patterns of the mean VAS scores recorded on passive movement until rescue analgesia were very similar to those recorded at rest."

Because there was no formal statistical comparison of the VAS pain scale, the sponsor's description of the results highlights the more favorable aspects of their product. The statistical review, however, describes the results more objectively, i.e., the group found to have the highest VAS score and height of sensory block. Please note the statistical review of these efficacy measurements.

Height of Sensory Block

... the median and interquartile range values were S1 at all timepoints in both the left and right lower dermatomes. For the upper dermatomes, both left and right sides ... some variability was seen between the treatment groups with regard to the level of sensory block achieved.

* For both the left and right lower dermatomes all median values were calculated to be S1 and hence graphical output was deemed inappropriate.

[Item 8. Vol. 1.78, p. 058 – 059]

STUDY # 030428

PROTOCOL SYNOPSIS:

Title: "A Randomized Single Centre, Double-blind Parallel Group Study to Compare the Efficacy, Safety and Pharmacokinetics of 0.25% Levobupivacaine (S-enantiomer) with 0.25% Bupivacaine (racemic mixture) Given as Infiltration Anaesthesia in Patients Undergoing Elective Inguinal Hernia Repair"

Primary Objective: "To compare the pain relief achieved using 0.25% levobupivacaine with that achieved using 0.25% racemic bupivacaine when used for infiltration anaesthesia"

Secondary Objective: (1) "To determine the plasma concentrations of levobupivacaine and bupivacaine following dosing of 0.25% levobupivacaine with 0.25% racemic bupivacaine", and, (2) To evaluate the relative safety profiles of the 2 different formulations"

[Item 8, Vol. 1.81, p. 023]

Study Design:

The study is designed as a randomized, double-blind, parallel group comparative study of the efficacy, safety and pharmacokinetics of 0.25% levobupivacaine with 0.25% racemic bupivacaine in patients scheduled for elective inguinal hernia repair under regional anesthesia. The protocol calls for two groups of thirty patients to each be randomly assigned to one of two treatment arms.

Group I	0.25% levobupivacaine
Group II	0.25% bupivacaine

Eligible patients will be ASA Class I or II males between 30 and 80 years of age, consenting to receive regional anesthesia for an uncomplicated elective inguinal hernia repair. Patients must have no prior history of systemic illness, drug or alcohol abuse within the previous 6 months, not received an investigational drug or vaccine in the previous 28 days, found to have a combined indirect/direct hernia or femoral hernia during surgery, or be female.

Eligible patients underwent a brief screening phase followed by a 1:1 randomization (30 patients per group) to receive either 0.25% levobupivacaine or 0.25% bupivacaine via open field block anesthesia. A total of 50 ml of study drug was used to infiltrate the skin and subcutaneous tissue of the area to be incised. An additional 10 ml (maximum) of study drug was allowed, if needed, to infiltrate the wound peri-operatively. Eight-ml of study drug was then administered intracutaneously along the line of incision followed by 12 ml in the deeper layers under the incision.

Following the incision, an additional 20-ml was administered subfascially, near the pubic bone and around the cord at the deep inguinal ring. The remaining 10 ml was administered, as needed, during the dissection or at the latest in the muscle layers during the suturing of the mesh to the conjoined tendon. If, thereafter, any additional analgesia was needed, a maximum of 10 ml was allowed.

Immediately following surgery, patients completed a global verbal rating scale of any pain experienced during surgery using a 4-point scale (nil, slight, moderate, or severe) and a VAS scale of satisfaction with the anesthetic received. Post-operatively, patients also completed a VAS scale at 1, 2, 3, 4, 8, 12, 24, 36, and 48 hours post-injection. These assessments were made while the patients were supine, rising from the supine to sitting position, and while walking.

All patients were prescribed ibuprofen 600 mg TID for 4 days post-injection. The time to first intake of ibuprofen and the amount taken was recorded. A total of 13 blood samples were taken from 20 patients to measure levobupivacaine and bupivacaine serum concentrations. Samples were drawn from the cannula sited in the contralateral arm to any intravenous infusions the patient was receiving. The samples were taken pre-dose, immediately before the second, third and fourth administration of study drug, and at 5, 15, 30, 45, 60 min, 1.5, 2, 3, and 4 hours after completion of the injection. Time 0 was determined to be after completion of the fourth injection.

Table 119. Schedule of Assessments

2.2 Study assessments

			Timepoint (Post completion of injection)																			
	Pre-surgery	Surgery	Minutes							Hours							Discharge **	Hours				
			0	5	10	15	20	30	45	1	1.5	2	2.5	3	3.5	4		6	8	12	24	36	48
Consent	X																						
Pre-surgery assessments*	X																						
Vital signs	X				X		X	X		X	X	X	X	X	X	X							
Pulse oximetry	X																						
Continuous (Lead II) ECG*	X	X	X	X	X	X	X	X															
Visual Analogue Scale		X#								X		X		X		X			X	X	X	X	X
PK sample +	X	X@		X		X		X	X	X	X	X		X		X							
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
12-lead ECG	X																						
Urinalysis	X																						
Return Ibuprofen pack/diary card																							X

* Full medical history, physical examination, height, weight and details of any regular medication.
** 4h post-surgery, if appropriate.
\+ In 20 patients only.
\# Immediate post-operative VAS of satisfaction with anaesthetic and global rating scale of peri-operative pain.
* Rhythm strips have been produced at 15 minute intervals during the time the continuous ECG was in place.
@ Immediately before the second, third and fourth administration of the test compound.

Note : On admission to the anaesthetic room, continuous ECG monitoring (Lead II), non-invasive arterial pressure monitoring and pulse oximetry were to have been established.

[Sponsor's Table 2.2, "Study Assessments", Item 8, Vol. 1.81 p. 026]

STATISTICAL ANALYSIS

"The primary measure of efficacy was defined as the randomized area under the VAS vs time curve over all available assessments (i.e., area under the curve divided by the assessment time)."

"The objective of this study was to compare the 2 study drugs with regard to pain relief. From a previous parallel group study in a similar group of patients, VAS scores ranged from zero to 60 mm. It was therefore reasonable to estimate the between patient standard deviation as 15 mm. Using this estimate, $\alpha = 0.05$, $\beta = 0.2$ and the largest difference to be detected set to 10 mm, the required sample size was calculated to be 33 evaluable patients per group."

"The primary analysis population for efficacy in this study was the Intent-to-Treat population. Confirmatory analyses on all efficacy variables have been performed using the per-protocol population."

"All patients classed as 'major' protocol violators have been excluded from the per-protocol analysis. A list of 'major' protocol violations was constructed in order to define this population, before breaking of the study blind. One further criterion necessary for inclusion in this population was that patients should have had at least 24 h of VAS measures of which at least 66% were available."

"All patients who were randomised and who received the study medication formed the safety population. The intent-to-treat population included all randomised patients (including protocol violators) but excluded the following:

- patients who did not receive any of the randomised study medication.
- patients who during the study, were found to have a combined indirect/direct hernia or femoral hernia."

[Item 8, Vol. 1.81 p. 041-043]

ne intended analysis was as follows:

"The primary measures of efficacy were defined to be the normalised area under the VAS (at rest in the supine position, rising from the supine to the sitting position and walking) vs time curve over all available assessments (ie area under the curve divided by the assessment time) using the 'intent-to-treat' population."

"Each of the above response variables was to be analysed using analysis of variance (ANOVA) with terms for treatment. The consumption of relief medication (ie ibuprofen) was to be considered as a covariate. Using the error variance from the ANOVA, comparison of the treatment means was to be made using a Student's 't'-test. Estimates of treatment difference and the associated 95% confidence interval were to be calculated."

"If necessary, the analysis of the primary measures of efficacy was to be repeated using the 'intent-to-treat' population but excluding any patients who received more than 50 ml of the study drug."

"In addition to the VAS described above, a secondary measure of efficacy was defined as the VAS of satisfaction with the anaesthetic measured immediately following completion of surgery. This response was to be analysed using identical methods as described above ie ANOVA."

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

"In addition to the formal statistical analyses, mean VAS (at rest rising from the supine to the sitting position and walking) measurements recorded at each timepoint were to be illustrated graphically."

"The global verbal rating scale of pain experienced during surgery was to be compared between treatments using logistic regression."

"All statistical analyses were to be performed using both 'intent-to-treat and 'per-protocol' populations 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, was to be included in such a way as to minimise bias."

[Item 8, Vol. 1.81 p. 046-047]

.anges in the Conduct of the Planned Analyses

"Categorical data have been presented using counts and percentages, while continuous variables have been presented using the mean, standard deviation, range and number of subjects. Missing values have been displayed as appropriate. Minimums and maximums have been quoted to the number of decimal places recorded in the CRF; means and standard deviations have been quoted to one further decimal place. Percentages have been rounded to one decimal place, and there were occasions when the total of the percentages did not equal 100% exactly, but were 99.9% or 100.1% for example. P-values $\geq$ 0. I have been quoted to 2 decimal places, while p-values < 0.1 have been quoted to 3 decimal places."

"A significance level of 5% has been used throughout and all p-values given were the result of two-sided tests. Thus, any test result producing a p-value of less than 5% (or 0.05) has been considered statistically significant. Differences between the 2 treatment groups have been estimated as 'levobupivacaine-bupivacaine'. Odds have been calculated as levobupivacaine/bupivacaine. The differences between levobupivacaine and bupivacaine have been estimated from the analysis and 95% confidence intervals have been constructed around the estimated differences. In all cases changes from baseline have been calculated as 'treatment-baseline'."

[Item 8, Vol. 1.81 p. 048-049]

PROTOCOL AMENDMENT:

The following amendments were dated 3/24/97 and 6/19/97. They consist of following changes:

1. Inclusion Criteria
   - Ages of males included have been changed from 35-70 years to 30-80 years.

2. Randomization and Blinding
   - The sponsor has added a full description of the procedure used in assigning patient numbers. It is as follows: "... non-pharmacokinetic patient will be assigned the lowest number available and the pharmacokinetic patients will be assigned the highest number available..."

3. Administrative Changes
   - Supplier for Ibuprofen has been declared
   - Follow-up procedure for patients unable to return their diary post-operatively
   - Editorial changes

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 67 patients randomized, 66 (98.5%) received study medication and were considered to be evaluable for the safety analyses. Of the 67 patients randomized, 1 patient (randomized to the bupivacaine group) was withdrawn prior to study drug administration. Patient 004 did not have a hernia.

Of the 66 patients who received the study drug, all 66 patients were found not to have a combined indirect/direct inguinal hernia or femoral hernia and therefore were included in the Intent-to-Treat population.

However, 10 patients from the levobupivacaine group and 11 from the bupivacaine group committed major protocol violations and were excluded from the per-protocol population. Protocol violations in the bupivacaine group included: Patient 004 who did not have a hernia, Patient 036 who had a recurrent hernia, and Patients 003,012,014, 016, 023, 040, 045, 060, and 077 who received prohibited analgesics/anesthetics during or after surgery. In the levobupivacaine group, all violations occurred due to patients receiving prohibited analgesics/anesthetics during or after surgery (Patients 001,002, 007, 019, 020, 021, 033, 034, 038, and 067).

Table 120. Patient – Specific Protocol Violations

PATIENT NUMBER/CENTER	TREATMENT GROUP	VIOLATION	PATIENT TOTALS N (%)
			67 (100) Randomized
Excluded from Safety Population:			**66 (98.5) Safety Population**
004	Bupivacaine (Not Treated)	Patient Did Not Have A Hernia	
Excluded from Intent-to-Treat:			**66 (98.5) Intent-to-Treat**
None			
Excluded from Per-Protocol:			**46 (68.6) Per-Protocol**
036	Bupivacaine	Patient Had a Recurrent Hernia	
003,012,014, 016, 023, 040, 045, 060, and 077	Bupivacaine	Received Prohibited Analgesics/Anesthetics	
001,002, 007, 019, 020, 021, 033, 034, 038, and 067	Levobupivacaine	Received Prohibited Analgesics/Anesthetics	
Other Violations: (not withdrawals)			
013	Levobupivacaine	Mild Neurological Disorder	
022	Levobupivacaine	Completed GVRS[12] before Surgery End	
003	Bupivacaine		
074, 078	Levobupivacaine	Blood Samples Taken After Second and Fourth Injections, Respectively	
21 (31.3 %) Total Withdrawals			**46 (68.7%) Total Completed**

[12] GVRS – Global Verbal Rating Scale of Satisfaction with the Anesthetic

Table 121. Patient Disposition

TABLE 6 LEVOBUPIVACAINE - 030428

Summary of formation of populations

by treatment group

Total population

Evaluation group	Levobupivacaine (n=33)	Bupivacaine (n=34)
Total population	33 (100.0%)	34 (100.0%)
Safety population	33 (100.0%)	33 (97.1%)
Intent-to-treat population	33 (100.0%)	33 (97.1%)
Per-protocol population	23 (69.7%)	23 (67.6%)

[Sponsor's Table 6, Item 8, Vol. 1. 81, p. 108]

APPEARS THIS WAY
ON ORIGINAL

emographics

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

Table 122. Demographics - Intent–to Treat Evaluable Population

TABLE 7 LEVOBUPIVACAINE - 030428

Demographic details

by treatment group

Intent-to-treat population

Variable		Levobupivacaine (n=33)		Bupivacaine (n=33)	
Age (years)	mean	57.4		56.4	
	sd	15.7		14.8	
	minimum	30		31	
	maximum	79		78	
	n	33		33	
Race	white	33	(100.0%)	33	(100.0%)
	black	0	(0.0%)	0	(0.0%)
	hispanic	0	(0.0%)	0	(0.0%)
	asian	0	(0.0%)	0	(0.0%)
	other	0	(0.0%)	0	(0.0%)
Height (cm)	mean	174.5		176.1	
	sd	8.7		6.0	
	minimum	161		164	
	maximum	190		187	
	n	33		33	
Weight (kg)	mean	74.00		76.31	
	sd	12.47		8.70	
	minimum	50.3		59.0	
	maximum	99.5		100.0	
	n	33		33	

[Sponsor's Table 7, Item 8, Vol.1.81, p. 109]

emographic trends were similar in both treatment groups in the Intent-to-Treat population. All patients were White. Patients in the levobupivacaine group were slightly older (mean of 57.4 years, SD=15.7) than the bupivacaine group (mean of 56.4 years, SD = 14.8). The mean height in the levobupivacaine group was 174.5 cm (SD 8.7) and 176.1 cm (SD=6.0) was the mean height in the bupivacaine group. The mean weight was slightly higher in the bupivacaine group (mean of 76.31 kg, SD=8.70) than the levobupivacaine group (mean of 74.00 kg, SD = 12.47).

Patients in the per-protocol population were broadly similar to those in the Intent-to-Treat population. The patients in the levobupivacaine group on average were older (mean 62.2 years, SD 14.5 years) than those in the bupivacaine group (mean 56.6 years, SD 15.8 years).

'In the levobupivacaine group, 27 patients (81.8%) reported 73 significant medical histories between them. Similarly, 27 patients (81.1%) in the bupivacaine group reported 95 significant medical histories. Of these,14 patients (42.4%) in the levobupivacaine group had 25 significant medical histories that were still present and 16 patients (48.5%) in the bupivacaine group had 23 continuing significant medical histories"

"The 3 most frequently occurring body systems were 'circulatory system digestive system' and 'genitourinary system'. Many of the patients with medical histories under these body systems had a disease still present. The largest difference between treatment groups was under the body system 'digestive system', where 13 patients in the levobupivacaine group (39.4%) and 19 *(57.6%)* in the bupivacaine group reported having a significant medical/surgical history. For the majority of body systems, the treatment groups appeared to be similar in terms of the number and percentage of patients with significant medical histories under each body system."

"The number of abnormal results from the physical examination was exactly the same in the levobupivacaine and bupivacaine groups. For one body system ('lungs'), all results from those patients examined were found to be normal. As was to be expected, all patients in the intent-to-treat population for whom the abdomen was examined, had an abnormal result." For all but 3 of the body systems (namely 'lungs', 'heart' and 'abdomen'), at least 90% of patients were not examined."

"All patients in both the levobupivacaine and bupivacaine groups took at least one concomitant medication before injection. All 33 patients (100%) in the levobupivacaine group reported taking 83 concomitant therapies between them and all 33 patients (100%) in the bupivacaine group reported taking 78 concomitant therapies before injection."

"All patients recorded a central nervous system concomitant medication before injection. This is because the pre-medication midazolam fell into this category."

[Item 8, Vol. 1.81, p. 074-077]

Table 123. Medical History Details

TABLE II

Medical/Surgical History Details

ICD-9 Body System Procedures in Medicine	Treatment			
	Levobupivacaine		Bupivacaine	
	N	%	N	%
Infectious and parasitic disease	1	3.0	0	0.0
Neoplasms	2	6.1	3	9.1
Endocrine, nutritional, metabolic, immunity	1	3.0	1	3.0
Mental disorders	3	9.1	0	0.0
Nervous system and sense organs	3	9.1	6	18.2
Circulatory system	8	24.2	10	30.3
Respiratory system	3	9.1	3	9.1
Digestive system	13	39.4	19	57.6
Genitourinary system	6	18.2	4	12.1
Skin and subcutaneous tissue	1	3.0	0	0.0
Musculoskeletal system and connective tissue	3	9.1	2	6.1
Congenital anomalies	0	0.0	1	3.0
Symptoms, signs and ill-defined conditions	5	15.2	2	6.1
Injury and poisoning	0	0.0	3	9.1
Other procedures for diagnosis	0	0.0	1	3.0
Radiography	0	0.0	1	3.0

[Sponsor's Table II. Item 8. Vol. 1.81 p. 076]

\fter 'central nervous system', the 2 most common body systems under which patients reported taking pre-jection concomitant therapies were 'blood and blood forming organs' and 'musculoskeletal system'. Two patients in the levobupivacaine group (6.1%) and no patients in the bupivacaine group) reported taking therapies for the 'blood and blood forming organs' body system. One patient (3.0%) in the levobupivacaine group and no patients in the bupivacaine group took musculoskeletal system drugs."

"Most continuing medications were those which acted on the 'cardiovascular system' or the 'central nervous system'. Five patients in the levobupivacaine group (15.2%) and 4 in the bupivacaine group (12.1%) reported taking therapies for the 'cardiovascular system'. Four patients in the levobupivacaine group (12.1%) and one patient in the bupivacaine group (3.0%) reported taking therapies for the central nervous system'."

"Many more concomitant therapies were reported to be taken after the injection. Thirty one patients (93.9%) in the levobupivacaine group reported taking 162 concomitant therapies and 27 patients (81.8%) in the bupivacaine group reported taking 142 therapies. The majority of patients who took concomitant therapies during the post-injection period took at least one drug for the 'musculo-skeletal system'. This was because many patients took pain relief medication (eg ibuprofen) after the injection. The second most common body system under which patients took concomitant therapy was 'central nervous system'. Ten patients (30.3%) in the levobupivacaine group and 9 (27.3%) in the bupivacaine group took such drugs."

"Thirty three patients were dosed in the levobupivacaine group and 33 in the bupivacaine group. Apart from Subject 80, all patients received 50 ml of either 0.25% levobupivacaine or 0.25% bupivacaine. Subject 080 received only 46 ml of bupivacaine due to spillage of the 4 th dose. In addition 5 patients (15.2%) in the levobupivacaine group received up to 10 ml of additional study drug compared to 3 patients (9.1%) in the bupivacaine group."

[Item 8. Vol. 1.81, p. 078 – 080]

ponsor's Efficacy Results:

Primary Efficacy Measurement

Normalized Area Under Supine VAS for Post-Operative Pain vs. Time Curve

"The mean normalised area under the curve was slightly lower in the bupivacaine group (10.687 mm, SD 9.222 mm) than in the levobupivacaine group (12.505 mm, SD 15.338 mm). No statistically significant difference was detected between the treatments (p=0.63) after adjusting for normalised dosage of relief medication."

"The estimate of treatment difference on the square root transformed data, adjusted for normalised dosage of relief medication, was 0.194 mm. A value equal to zero would signify no treatment difference. The 95% confidence interval surrounding this estimate was (-0.994, 0.606)."

"For the per-protocol population, the difference between the means was smaller with the mean normalised area under the curve in the levobupivacaine group being 9.433 mm (SD 11.847) and that in the bupivacaine group being 9.210 mm (SD 8.735)."

"Again, treatment group was found to be non-significant (p=0.25 after adjusting for normal- ised dosage of relief medication). The square root transformed, adjusted, adjusted estimate for treatment difference was 0.550 mm and the corresponding 95% confidence interval (-1.494, 0.394)."

Supine VAS Scores for Post-operative Pain

"The maximum mean supine VAS score was in the levobupivacaine group at the 24 h assessment (15.8 mm, SD 20.6 mm) compared to 10.6 mm, SD 12.0 mm in the bupivacaine group. The mean maximum VAS score in the bupivacaine group was observed at 12 h (13.9 mm, SD 12.7 mm). It should be noted that for the 1-4 h VAS assessments, the results observed in the bupivacaine group were consistently higher than those in the levobupivacaine group. However, from 8-48 h post dose this trend was reversed."

"The mean maximum VAS scores were observed at 12 h and 24 h for the bupivacaine group (12.3 mm, SD 11.8 mm) and the levobupivacaine group (11.5 mm, SD 16.5 mm), respectively."

The statistical analysis of this endpoint is found above i.e., the normalized normalized area under supine VAS for post-operative pain vs. time curve.

[Item 8, Vol. 1.81. p. 080 – 082]

Rising VAS Scores for Post-operative Pain

"Mean VAS scores recorded while patients in the intent-to-treat population were rising from the lying to sitting position were greater than those recorded in the supine position. There was no clear trend in terms of one treatment group being superior with regard to this variable."

"The mean lying to sitting VAS scores for the per-protocol population were lower than those reported in the intent-to-treat population. Again, the mean values were similar between treatment groups."

The statistical analysis of this endpoint is found below, i.e., the normalized area under lying to sitting VAS for post-operative pain vs. time curve.

Normalized Area Under Lying to Sitting VAS for Post-operative Pain vs. Time Curve

"The mean normalised area under the lying to sitting VAS curve was similar between treatment groups. The mean for the levobupivacaine group was 16.721 mm (SD 15.990) compared to 16.456 mm (SD 15.897) in the bupivacaine group."

"Unsurprisingly, no statistically significant difference was detected between the mean square-root transformed data of the 2 treatment groups when adjusted for normalised dosage of relief medication (p=0.70). The estimate for treatment difference (transformed and adjusted) was 0.163 mm. The 95% confidence interval surrounding this was (-0.996, 0.670)."

"As for the intent-to-treat population, the mean values for the per-protocol population were very similar between treatment groups. The mean observed value in the levobupivacaine group was 13.386 mm (SD 14.264) and the mean observed in the bupivacaine group was 13.335 mm (SD 13.767)."

"There was no significant difference detected between the treatment groups (p=0.47). The adjusted estimate for treatment difference on the transformed data was 0.378 mm and the corresponding 95% confidence interval was (-1.418, 0.661)."

Walking VAS Scores for Post-operative Pain vs. Time Curve

"Mean walking VAS scores were consistently lower in the levobupivacaine group than in the bupivacaine group. The largest difference between the mean scores of the two groups was observed at 36 h post-injection. The mean score in the levobupivacaine group at 36 h was 13.5 mm (SD 15.7) compared to 20.8 mm (SD 19.6) in the bupivacaine group ."

"In the per-protocol population, the mean walking VAS scores were slightly lower than in the intent-to-treat population. At all but the first visit, the values for the levobupivacaine group were consistently lower than those in the bupivacaine group."

The statistical analysis of this endpoint is found below, i.e., the normalized area under walking VAS for post-operative pain vs. time curve.

[Item 8, Vol. 1.81, p. 083 – 085]

Table 124. Analysis of Primary Outcome Measurement

TABLE 17 LEVOBUPIVACAINE - 030428

Summary and analysis of normalised area under supine VAS for post-operative pain vs time curve

by treatment group

Intent-to-treat population

Supine VAS		Levobupivacaine (n=33)	Bupivacaine (n=33)
Normalised area under curve (mm)	mean	12.505	10.687
	sd	15.338	9.222
	minimum	0.04	0.02
	maximum	58.69	35.74
	n	33	33

NB: VAS scale 0mm = no pain, 100mm = worst pain imaginable

Analysis of variance test gives a treatment p-value of 0.63

Difference in treatment means of square root transformed data (adjusted for normalised dosage relief medication) is -0.194mm
Corresponding 95% confidence interval for difference between transformed treatment means is (-0.994, 0.606)

Differences between the two treatment groups have been estimated as 'levobupivacaine - bupivacaine'.

Table 125. Analysis of Primary Outcome Measurement

TABLE 21 LEVOBUPIVACAINE - 030428

Summary and analysis of normalised area under lying to sitting VAS for post-operative pain vs time curve

by treatment group

Intent-to-treat population

Lying to sitting VAS		Levobupivacaine (n=33)	Bupivacaine (n=33)
Normalised area under curve (mm)	mean	16.721	16.456
	sd	15.990	15.897
	minimum	0.18	0.00
	maximum	58.98	62.36
	n	33	33

NB: VAS scale 0mm = no pain, 100mm = worst pain imaginable

Analysis of variance test gives a treatment p-value of 0.70

Difference in treatment means of square root transformed data (adjusted for normalised dosage relief medication) is -0.163mm
Corresponding 95% confidence interval for difference between transformed treatment means is (-0.996, 0.670)

Differences between the two treatment groups have been estimated as 'levobupivacaine - bupivacaine'.

[Sponsor's Table 17 and 21, Item 8, Vol. 1.81, p. 130 and 138 respectively]

Table 126. Analysis of Primary Outcome Measurements

TABLE 25 LEVOBUPIVACAINE - 030428

Summary and analysis of normalised area under walking VAS for post-operative pain vs time curve

by treatment group

Intent-to-treat population

Walking VAS		Levobupivacaine (n=33)	Bupivacaine (n=33)
Normalised area under curve (mm)	mean	13.892	16.946
	sd	14.857	13.850
	minimum	0.00	0.00
	maximum	59.08	45.94
	n	33	33

NB: VAS scale 0mm = no pain, 100mm = worst pain imaginable

Analysis of variance test gives a treatment p-value of 0.064

Difference in treatment means of square root transformed data (adjusted for normalised dosage relief medication) is -0.736mm
Corresponding 95% confidence interval for difference between transformed treatment means is (-1.516, 0.044)

Differences between the two treatment groups have been estimated as 'levobupivacaine - bupivacaine'.

[Sponsor's Table 25, Item 8, Vol. 1.81, p. 146]

Normalised Area Under Walking VAS for Post-operative Pain vs. Time Curve

"For the intent-to-treat population, the mean normalised area under the walking VAS curve was lower in the levobupivacaine group than in the bupivacaine group. These values were 13.892 mm (SD 14.857) in the levobupivacaine group and 16.946 mm (SD 13.850) in the bupivacaine group."

"The model described in Section 7.9.4.1 produced a p-value for treatment group that was non-significant at the 5% level (p=0.06). The transformed, adjusted estimate for treatment difference was 0.736 mm and the corresponding 95% confidence interval was (-1.516, 0.044).

"Mean values in the per-protocol population were lower than those in the intent-to-treat population. The mean normalised area under the walking VAS curve in the levobupivacaine group was 9.228 mm (SD 10.826) compared to 13.655 mm (SD 12.474) in the bupivacaine group."

"A statistically significant difference was found to exist between treatment groups (p=0.019) when the model was fitted. The transformed, adjusted estimate for treatment difference was 1.134 mm and the corresponding 95% confidence interval was (-2.070, -0.198)."

[item 8, Vol. 1.81, p. 085 –087]

Secondary Efficacy Measurements:

VAS of Satisfaction with the Anesthetic

"For the intent-to-treat population, the mean VAS score of satisfaction with the anaesthetic was seen to differ slightly between the treatment groups. In the levobupivacaine group, the mean was 72.9 mm and in the bupivacaine group it was 78.6 mm."

"The observations for the 2 treatment groups were found not to be statistically significantly different (p=0.17). The estimate for the difference in treatment group means was -5.8 mm, with a 95% confidence interval of (-14.1, 2.6)."

"For the per-protocol population, the mean VAS score was slightly lower in the levobupivacaine group than in the bupivacaine group (76.7 mm compared to 79.6 mm)."

"Again, this difference was not significant at the 5% level (p=0.50). The estimate of treatment group difference in the per-protocol population was -2.9 mm, lower than the Intent-to-treat population. The 95% confidence interval constructed around this estimate was (-11.5, 5.7)."

[item 8, Vol. 1.81, p. 085 –087]

Global Verbal Rating Scale of Pain Experienced During Surgery

More patients in the levobupivacaine group reported 'moderate or 'severe' pain during surgery than patients in the bupivacaine group. Ten patients (30.3%) in the levobupivacaine group and 7 (21.2 %) in the bupivacaine group reported 'moderate' pain during surgery. Two patients (6.1%) in the levobupivacaine group reported 'severe' pain during surgery compared to none in the bupivacaine group."

"A logit model was fitted ... and treatment group was found not to be statistically significant at the 5% level (p=0.17). The odds ratio for treatment group was favourable towards bupivacaine (odds ratio = 0.505). That is, a patient taking levobupivacaine was estimated to be around half as likely as one in the bupivacaine group to record 'nil' pain during surgery. The 95% confidence interval for this odds ratio was (0.189, 1.347)."

"As for the intent-to-treat population, most patients in the per-protocol population reported feeling 'slight' pain during surgery. These figures were 13 patients (56.5%) in the levobupivacaine group and 15 (65.2%) in the bupivacaine group."

"Treatment group was non-significant in the logit model (p=0.29). The odds ratio for levobupivacaine over bupivacaine was 0.531, and its corresponding 95% confidence interval was (0.164, 1.720)."

Normalized Dosage of Relief Medication

"The median normalised dosage of relief medication was similar between treatment groups. In the levobupivacaine group the median value was 50.509mg.h and in the bupivacaine group this value was 50.526 mg.h"

Wilcoxon's two-sample test produced a p-value equal to 0.55. The estimate of median treatment difference was 0.040 mg.h and the corresponding 95% confidence interval was (-0.581, 24.813).

"For the per-protocol population, the median normalised dosage of relief medication was identical between treatment groups (37.895 mg.h)"

"Wilcoxon's two-sample test produced a p-value equal to 0.24. The median difference between treatments was calculated as 12.618 mg.h and its 95% confidence interval was (-0.089, 25.232).

[Item 8, Vol. 1.81, p. 087 – 088]

Table 127. Analysis of Secondary Outcome Measurement

TABLE 28

LEVOBUPIVACAINE - 030428

Summary and analysis of VAS scores for satisfaction with the anaesthetic

by treatment group

Intent-to-treat population

VAS scores (mm)		Levobupivacaine (n=33)	Bupivacaine (n=33)
VAS scores for satisfaction with anaesthetic	median	77.0	80.0
	mean	72.9	78.6
	sd	18.6	15.3
	minimum	25	36
	maximum	99	100
	n	33	33

NB: VAS score 0mm - extremely unsatisfied, 100mm - extremely satisfied

Analysis of variance test gave a treatment p-value of 0.17

Difference in treatment means was -5.8mm
Corresponding 95% confidence interval for difference between treatment means was (-14.1, 2.6)

Differences between the two treatment groups have been estimated as 'levobupivacaine - bupivacaine'.

Table 128. Analysis of Secondary Outcome Measurement

TABLE 30

LEVOBUPIVACAINE - 030428

Summary and analysis of global verbal rating scale of pain experienced during surgery

by treatment group

Intent-to-treat population

Scale of pain		Levobupivacaine (n=33)	Bupivacaine (n=33)
Global verbal rating scale of pain experienced during surgery	nil	3 (9.1%)	4 (12.1%)
	slight	18 (54.5%)	22 (66.7%)
	moderate	10 (30.3%)	7 (21.2%)
	severe	2 (6.1%)	0 (0.0%)

Logit model provided a p-value for treatment difference of 0.17

The odds ratio for treatment group was 0.505
The corresponding 95% confidence interval was calculated as (0.189, 1.347)

Odds ratios have been calculated as levobupivacaine/bupivacaine.

[Sponsor's Tables 28 and 30, Item 8, Vol. 1.81, p. 149-151]

ne to First Dose of Relief Medication

"Eight patients in the intent-to-treat population did not take any relief medication up to the 48 h assessment and hence were included in this analysis as censored observations. Two of these patients were in the levobupivacaine group and the remaining 6 were in the bupivacaine group. When the censored observations were included, the median [mean] time to first dose of relief medication was slightly lower in the levobupivacaine group (6.85 h) [11.22] than in the bupivacaine group (7.05 h) [14.67]. The median [mean] time when censored observations were excluded was higher in the levobupivacaine group (6.83 h) [8.84] than in the bupivacaine group (5.43 h) [7.26]. This change in the trend was due to the larger number of censored observations in the bupivacaine group."

"The log-rank test for the difference between the time to first dose in each treatment group in the intent-to-treat population produced a p-value of 0.45 that was non-significant at the 5% level."

"Overall, summary statistics for the per-protocol population showed a longer time to first dose of relief medication than for the intent-to-treat population. Both with and without censored observations, the median time to first dose of relief medication was slightly lower in the levobupivacaine group than in the bupivacaine group. These values were 8 h and 7.82 h in the levobupivacaine group and 9.23 and 7.83 h in the bupivacaine group."

"Again, the log-rank test produced a non-significant result (p=0.27) showing that there was no evidence to suggest that the time to first dose of relief medication was different between treatment groups in the per-protocol population."

\S Scores for Post-operative Pain up to the First Request for Relief Medication

"Four patients in the intent-to-treat population (2 in each treatment group) could not be included in these analyses because they requested relief medication before or at the +1 h assessment."

The statistical analysis of this endpoint is found below, i.e., normalized area under supine VAS for post-operative pain vs. time curve up to first request for relief medication.

Normalized Area Under Supine VAS for Post-operative Pain vs Time Curve up to First Request for Relief Medication

"For the intent-to-treat population, the median [mean] normalised area under the curve was lower in the levobupivacaine group (1.813 mm) [5.520] than in the bupivacaine group (3.171 mm) [7.035]. Wilcoxon's two-sample test showed that this difference was not significant at the 5% level (p=0.27) The difference between median values of the treatment groups was greater in the per-protocol population, with the median in the levobupivacaine group reduced to 1.662 mm and that in the bupivacaine group being increased to 3.217 mm. Again, this difference was not significant at the 5% level (p=0.28). The estimate for the median difference between treatment groups was (-1.222 mm) with a 95% confidence interval of (-5.499, 0.351)."

[Item 8. Vol. 1.81, p. 088 – 090]

Table 129. Analysis of Secondary Outcome Measurement

TABLE 34

LEVOBUPIVACAINE - 030428

Summary and analysis of time to first dose of relief medication

by treatment group

Intent-to-treat population

Relief medication		Levobupivacaine (n=33)	Bupivacaine (n=33)
Time (hrs) to first dose (including censored patients)	mean	11.22	14.67
	25th percentile	4.83	4.33
	median	6.85	7.05
	75th percentile	11.23	12.15
	interquartile range	6.4	7.8
	n	33	33
Censored patients	uncensored observations	31 (93.9%)	27 (81.8%)
	censored observations	2 (6.1%)	6 (18.2%)
Time (hrs) to first dose (not including censored patients)	mean	8.84	7.26
	25th percentile	4.43	4.12
	median	6.83	5.43
	75th percentile	8.58	8.37
	interquartile range	4.2	4.3
	n	31	27

N.B. The time of the 48 Hour assessment was used as the time to first dose of relief medication for censored observations.

The log-rank test between treatment groups produced a p-value of 0.45

[Sponsor's Tables 34, Item 8, Vol. 1.81, p. 155]

Table 130. Analysis of Secondary Outcome Measurements - Supine VAS vs. Time Curve VAS Up to First Dose of Relief Medication

TABLE 36 LEVOBUPIVACAINE - 030428

Summary and analysis of normalised area under supine VAS for post-operative pain vs time curve

VAS scores up to the first dose of relief medication

by treatment group

Intent-to-treat population

Supine VAS		Levobupivacaine (n=33)	Bupivacaine (n=33)
Normalised area under curve (mm)	median	1.813	3.171
	mean	5.520	7.035
	sd	8.866	8.748
	minimum	0.00	0.00
	maximum	38.77	35.25
	n	31	31
	missing	2	2

The four missing values were patients 1,2,3 and 16.
Patients 1,2 and 3 requested relief medication before the +1 Hour assessment.
Patient 16 requested relief medication at the +1 Hour assessment, hence the AUC was not calculable.
NB: VAS scale 0mm = no pain, 100mm = worst pain imaginable

Wilcoxon's two-sample test gave a p-value of 0.27

The estimate for the median difference between treatments was -0.021 mm
The corresponding 95% confidence interval was (-2.544, 1.810)

Differences between the two treatment groups have been estimated as 'levobupivacaine - bupivacaine'.

[Sponsor's Table 36, Item 8, Vol. 1.81, p. 157]

Normalized Area Under Lying to Sitting VAS for Post-operative Pain vs. Time curve Up to First Request for Relief Medication

"As for the supine VAS, the median normalised area under the curve was lower in the levobupivacaine group (2.307 mm) than in the bupivacaine group (3.358 mm) for the intent-to-treat population. However overall these values were higher than those recorded in the supine position. Wilcoxon's two-sample test showed that this difference was not significant at the 5% level (p=0.42). The estimate for the median difference between treatment groups was (0.016 mm) with a 95% confidence interval of (-2.073, 2.676)."

"The median normalised area under the curve was identical for the levobupivacaine group for the intent-to-treat population and the per-protocol population (2.307 mm). However, the median for the bupivacaine group was greater (5.157 mm). Wilcoxon's two-sample test produced a non-significant result (p=0.50) showing that there was no evidence to suggest that there was a difference between the 2 treatment groups in this analysis. The estimate for the median difference between treatment groups was (-0.668 mm) with a 95% confidence interval of (-5.698, 1.338)."

Normalized Area Under Walking VAS for Post-operative Pain vs. Time Curve up to First Request for Relief Medication

"In the intent-to-treat population, for VAS scores recorded while walking, prior to the first request of relief medication, the median [mean] normalised area under the curve in the levobupivacaine group (0.819 mm) [6.810] was lower than that in the bupivacaine group (4.697) [9.618]. However, this difference was not significant at the 5% level (p=0.100). The estimate for the median difference between treatment groups was (-0.329 mm) with a 95% confidence interval of (-3.994, 1.813)."

Number of Relief Medications Taken

"Patients in the levobupivacaine group took more relief medications per hour than those in the bupivacaine group. The mean number in the levobupivacaine group was 0.102 meds.h (S.D. 0.069) and in the bupivacaine group was 0.088 meds.h (S.D. 0.066). This difference was not found to be statistically significant (p=0.42)."

The statistical analysis of this endpoint is found in the sponsor's Table 42, "Summary and analysis of normalised number of relief medications taken by treatment group".''''

[Item 8. Vol. 1.81, p. 091 – 092]

Table 131. Analysis of Secondary Outcome Measurements – Lying to Sitting VAS vs. Time Curve VAS Up to First Dose of Relief Medication

TABLE 38 LEVOBUPIVACAINE - 030428

Summary and analysis of normalised area under lying to sitting VAS for post-operative pain vs time curve

VAS scores up to the first dose of relief medication

by treatment group

Intent-to-treat population

Lying to sitting VAS		Levobupivacaine (n=33)	Bupivacaine (n=33)
Normalised area under curve (mm)	median	2.307	3.358
	mean	7.124	8.195
	sd	10.258	9.908
	minimum	0.00	0.00
	maximum	39.68	40.42
	n	31	31
	missing	2	2

The four missing values were patients 1,2,3 and 16.
Patients 1,2 and 3 requested relief medication before the +1 Hour assessment.
Patient 16 requested relief medication at the +1 Hour assessment, hence the AUC was not calculable.
NB: VAS scale 0mm = no pain, 100mm = worst pain imaginable

Wilcoxon's two-sample test gave a p-value of 0.42

The estimate for the median difference between treatments was 0.016 mm
The corresponding 95% confidence interval was (-2.073, 2.676)

Differences between the two treatment groups have been estimated as 'levobupivacaine - bupivacaine'.

[Sponsor's Table 38, Item 8, Vol. 1.81, p. 159]