Table 132. Analysis of Secondary Outcome Measurements –

TABLE 40 LEVOBUPIVACAINE - 030428

Summary and analysis of normalised area under walking 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

Walking VAS		Levobupivacaine (n=33)	Bupivacaine (n=33)
Normalised area under curve (mm)	median	0.819	4.697
	mean	6.810	9.618
	sd	10.275	11.803
	minimum	0.00	0.00
	maximum	34.97	45.42
	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 0.100

The estimate for the median difference between treatments was -0.329 mm
The corresponding 95% confidence interval was (-3.994, 1.813)

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

[Sponsor's Table 40, Item 8, Vol. 1.81, p. 161]

Table 133. Analysis of Secondary Outcome Measurements – Number of Relief Medications Taken

TABLE 42

LEVOBUPIVACAINE - 030428

Summary and analysis of normalised number of relief medications taken

by treatment group

Intent-to-treat population

Normalised number of medications		Levobupivacaine (n=33)	Bupivacaine (n=33)
Normalised number of relief medications taken (meds/hr)	median	0.102	0.084
	mean	0.102	0.088
	sd	0.069	0.066
	minimum	0.00	0.00
	maximum	0.29	0.21
	n	33	33

Analysis of variance gave a p-value of 0.42

The estimate for treatment difference was 0.013 meds/hr
The corresponding 95% confidence interval was (-0.020, 0.047)

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

[Sponsor's Table 42, Item 8, Vol. 1.81, p. 163]

REVIEWER'S EFFICACY DISCUSSION

No significant differences were found between treatment groups for the primary efficacy variable - VAS for post-operative pain. Only one formal statistical test of efficacy was found to be significant at the 5% level - per-protocol analysis of the normalized AUC of walking VAS (p=0.019).

The clinical data has demonstrated that levobupivacaine is effective when administered as an inguinal nerve block following inguinal hernia repair. This conclusion is based upon the evidence that patients received some level of analgesia sufficient for inguinal hernia repair.

STUDY # 030721

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"

Verbal Rating Scale of Pain Experienced During Surgery

[Item 8, Vol. 1.83, p. 020]

APPEARS THIS WAY
ON ORIGINAL

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 $\geq$ 18 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 will undergo 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 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 10 cm VAS scale at the following times post completion of the third administration of study drug: 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hours. These assessments were made while the patients were supine, rising from the supine to sitting position, and while walking.

The surgeon was also asked to assess whether there was significant peri-operative bleeding (yes or no).

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 (or 14) 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, the end of the third administration of study drug (Time 0) and at 5, 15, 30, 45, 60 min, 1.5, 2, 3, 4, 5 and 6 hours after completion of the third injection. An eight hour sample was taken from those patients who remained in the hospital overnight.

Table 134. 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
Concomitant medication	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 packs/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, Item 8, Vol. 1.83, p.023]

STATISTICAL ANALYSIS

"The primary measures of efficacy were defined to be the normalised area under the VAS of post-operative pain (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)."

"Of secondary interest for the assessment of efficacy were:

- The VAS of satisfaction with the anaesthetic, measured immediately following completion of surgery.
- Global verbal rating scale of pain experienced during surgery.
- Normalised dosage of relief medication (Ibuprofen 600 mg tablets) over all available assessments (ie total dosage taken divided by the assessment time).
- Time to first dose of relief medication."

"The statistical hypothesis behind this trial was as follows:

H_0 the mean difference in the normalised area under the VAS of postoperative pain vs time curve over all available assessments between the treatment groups (levobupivacaine, bupivacaine) equals 0.

H_1: the mean difference in the normalised area under the VAS of postoperative pain vs time curve over all available assessments between the treatment groups (levobupivacaine, bupivacaine) does not equal zero."

. the following formal statistical analysis was performed:

Firstly, in order to obtain the primary measure of efficacy value for each patient, the following calculations were made:

1) The area under the VAS curve (AUC) for each patient was obtained using the trapezoidal rule, the area being calculated up to the last completed assessment (the n^{th} assessment). Supposing the VAS scores for any one patient at the 1,2, 3,4, 5, 6, 8, 12, 24, 36 and 48 h assessments were labeled VAS_1, VAS_2, VAS_3, VAS_4, VAS_5 - VAS_{36} and VAS_{48} respectively, and that each assessment was labeled t_1, t_2, t_3, t_4, t_5 - t_{36} and t_{48} respectively, then the formula for calculating a patient's AUC was as follows:

$$AUC = \frac{(VAS_1 + VAS_2)}{2}(t_2 - t_1) + \frac{(VAS_2 + VAS_3)}{2}(t_3 - t_2) + \ldots + \frac{(VAS_{n-1} + VAS_n)}{2}(t_n - t_{n-1})$$

[Item 8. Vol. 1.83, p. 045 –048]

"Note that the AUCs have been calculated using actual times the VAS measures were recorded, rather than target times. This was due to the fact that based on previous experience, it was anticipated that many patients would not record the VAS measures as per the target times identified in the diary card eg 2 h value was recorded 2.5 h after dosing etc. Any measures recorded later than 52 h after the third administration of test compound (ie a very late 48 h value) were excluded from the calculation".

2)"Then, in order to evaluate the normalised area under the VAS vs time curve, the AUC for a particular patient was divided by $(t_n - t_1)$. For example if the patient completed the study, the divisor would be $(t_{48} - t_1)=47$ (h)."

"Note again that actual rather than target times have been used in this calculation. However, if the actual time was missing then the target time was used."

3)"This value then was the primary measure of efficacy value for each patient.

4)"Note that missing values prior to withdrawal were replaced by linearly interpolated values; ie in general, if the i^{th} assessment was missing the following formula was used:

$$VAS_i = VAS_{i-1} + [\underline{VAS}_{i+1} - \underline{VAS}_{i+1}) \times (t_i - t_{i}]$$

$$(t_{i+1} - t_i)$$"

"Again, for the non-missing values, actual rather than target times have been used in this calculation."

5)"If the time was not completed for any particular assessment (supine, rising or walking) then the actual time for one of the other assessments at that timepoint was used in calculations if available. If the actual time was not entered for any of the 3 assessments, then the target times have been used. This convention was adopted since some patients failed to enter the actual time at which they were assessed for some or all of the assessments."

"The above response variable was to be analysed using analysis of variance (ANOVA) techniques, with terms for treatment, dose of study drug (ie 50 or 60 ml) and treatment by dose interaction. If the interaction term was not significant at the 10% significance level then this term was to be dropped from the model and the analysis repeated. The consumption of relief medication (ie ibuprofen) was also to be considered as a covariate. The residuals from this analysis were to be submitted to a Shapiro-Wilk test for normality and examined graphically to assess variance homogeneity. Any deviation from either assumption was to entail a re-analysis using an appropriate alternative transformation of the data eg log transformation. Furthermore, following examination of these data, non-parametric methods were to be used if the above methods were not considered appropriate."

[Item 8. Vol. 1.83, p. 048 - 050]

"In reality, the methodology differed from that detailed above due to the fact that dose of study drug was not ınsidered as a covariate."

" For the ibuprofen covariate, the value used in the ANOVA was again the normalised dosage taken over all available assessments, ie if a patient attended until the n^{th} assessment and the total number of tablets taken during that time was y, then the value used was:

$$\frac{V \times 600}{(t_n - t_{0.50})} \text{ mg}$$

where $t_{0.50}$ was used, as according to the protocol, Ibuprofen was to be taken a minimum of 30 min post-completion of the third administration of test compound. Some patients received medication from local supplies where each tablet was equal to 200 mg of Ibuprofen. These were Patients 1, 2, 147, 148 and 149. The calculation of normalised dosage of relief medication was adjusted accordingly for these patients. Note that, as above, the actual time t, of the n^{th} assessment was used rather than the target time. In addition, any tablets recorded later than 52 h after the third administration of test compound (ie a very late 48 h value) were excluded from the calculation."

"It was found that the raw data was not normally distributed. A model was fitted first with treatment group, consumption of relief medication and their interaction, and then with the interaction removed as it was non-significant at the 10% level. Examination of the residuals from this model suggested that a square-root transformation was appropriate. The log transformation was not used since this would result in patients with normalised AUC values of zero being excluded from the analysis. Also, the residuals from the model using the ⁻g-transformed data were not satisfactory. For all three VAS measurements (supine, rising (lying to sitting) and ılking) when the square-rooted data model was examined, the interaction term of treatment group with ıormalised dosage of relief medication was found to be non-significant at the 10% level and dropped from the analysis. Hence, the final analysis for each of the 3 VAS measurements modelled the square-rooted normalised AUC measurements with treatment group and normalised dosage of relief medication."

"In reality, the methodology differed from that described above due to the fact that dose of study drug was not considered as a covariate. The assumption of normality did not hold for the untransformed data nor for the data when it had undergone a square root transformation. Non-parametric methods were thus used to compare treatment groups, namely Wilcoxon's two-sample test. The estimate of treatment difference and associated 95% confidence interval were calculated based on Wilcoxon's two-sample test (Hollander and Wolfe, 1973)."

[Item 8. Vol. 1.83, p. 050 - 052]

VAS of Satisfaction with the Anesthetic

"An ANOVA was to be performed with terms for treatment, dose of study drug (ie 50 or 60 ml) and treatment by dose interaction. If the interaction term was not significant at the 10% significance level then this term was to be dropped from the model and the analysis repeated. The residuals from this analysis were to be submitted to a Shapiro-Wilk test for normality and examined graphically to assess variance homogeneity. Any deviation from either assumption was to entail a re-analysis using an appropriate alternative transformation of the data eg log transformation. Furthermore, following examination of these data, non-parametric methods were to be used if the above methods were not considered appropriate."

"In reality, the methodology differed from that described above due to the fact that dose of study drug was not considered as a covariate. The assumption of normality did not hold for the untransformed data nor for the data when it had undergone a square root transformation. Non-parametric methods were thus used to compare treatment groups, namely Wilcoxon's two-sample test. The estimate of treatment difference and associated 95% confidence interval were calculated based on Wilcoxon' 5 two-sample test."

Global Verbal Rating Scale of Pain Experienced During Surgery

"Another secondary measure of efficacy was the global verbal rating scale of pain experienced during surgery. Patients were asked to rate any pain experienced during surgery using a four point categorical scale (Nil, Slight, Moderate or Severe)."

"A logit model was to be fitted, with terms for treatment, dose of study drug (ie 50 or 60 ml) and the treatment by dose interaction. If the interaction term was not significant at the 10% significance level then this term was to be dropped from the model and the analysis repeated."

"The odds ratio estimate of treatment difference and the associated 95% confidence interval were to be calculated"

However, the methodology eventually used differed from that above for several reasons. Firstly, the covariate dose of study drug was dropped."

[Item 8. Vol. 1.83, p. 052 - 055]

Relief Medication

Other secondary measures of efficacy were the normalised dosage of relief medication (Ibuprofen 600 mg tablets) over all available assessments, and the time to first dose of relief medication."

"If a patient attended until the n^{th} assessment (at t_n hours post-third administration of test compound) and the total number of tablets taken during that time was y, then the normalised dosage was:

$$\frac{Y \times 600 \text{ mg}}{(t_n - t_{0.050})}$$

where $t_{0.50}$ was used because according to the protocol, Ibuprofen was to be taken a minimum of 30 min post-completion of the third administration of test compound."

"As previously mentioned, Patients 1,2, 147, 148 and 149 received medication from local supplies where each tablet was equal to 200 mg. The calculation of normalised dosage of relief medication was adjusted accordingly."

"... the normalised dosage was calculated using the actual time t, of the n^{th} assessment rather than target time. In addition, any tablets recorded later than 52 h after the third administration of test compound (ie a very late 48 h value) were excluded from the calculation. If a tablet was taken after the actual time t_n of the n^{th} assessment but within 52 h of the third administration of test compound then data for this tablet were included and t_n increased appropriately. If t_n was found to be greater than 52 h then it was truncated to 52 h for consistency. This method was adopted because some patients reported taking Ibuprofen after the 48 h assessment, and it was thought appropriate to expand the normalising time ($t_n - t_{0.5}$) to include the time that these extra tablets were ken."

"The mean and median normalised dosage (mg/h) of relief medication has been tabulated by treatment group, for both the intent-to-treat and per-protocol populations. In addition, for both populations, the following analysis was performed."

"The normalised dosage variable was to be analysed using analysis of variance (ANOVA) techniques, with terms for treatment, dose of study drug (ie 50 or 60 ml) and treatment by dose interaction. However, as explained above, the dose variable was not suitable for inclusion in the analysis. In addition, the assumption of normality did not hold for the normalised dosage, nor did it after a logarithmic and after a square root transformation. Comparisons between treatment groups were thus made using Wilcoxon's two-sample test. Estimates of treatment difference and corresponding 95% confidence intervals were calculated based on Wilcoxon's two-sample test."

"The time to first dose of relief medication has also been summarised by treatment group for both the intent-to-treat and per-protocol populations, showing the 25th percentile, median, and 75th percentile times (both including and excluding censored observations). The number of censored observations (ie no tablets recorded prior to completion/withdrawal) has been presented. A Kaplan-Meier curve has been produced, and the time to first dose compared between the treatment groups using the log rank test. Time values for censored observations were calculated as the time to the 48 h assessment."

[Item 8. Vol. 1.83, p. 055-057]

PROTOCOL AMENDMENT:

The following amendments were dated 2/28/97, 4/18/97 and 5/15/97. They consist of following changes:

1. Monitoring
   - Rhythm strips will no longer be produced at 15 minute intervals during the time that the continuous ECG is in place.
2. Pharmacokinetics
   - The sponsor has corrected the number of samples to be drawn from 14 (or 15) to 13 (or 14)
   - The sponsor has corrected the time for sampling from the end of the second and third dosing to the end of the third dosing only.
   - The sponsor has added the, "measured drug concentration vs. time curve" to include details of the pharmacokinetic modeling to be undertaken on the plasma concentration data produced.
3. Post-operative Periods
   - A 12-lead ECG will now be performed at the 48 hour follow-up visit
   - Follow-up procedure for patients unable to return their diary post-operatively
   - Editorial changes
4. Inclusion Criteria
   - Male patients aged 18 years or over will be included (previously males between 35 and 80 were included).

Table 135. Patient – Specific Protocol Violations

PATIENT NUMBER/CENTER	TREATMENT GROUP	VIOLATION	PATIENT TOTALS N (%)
			69 (100) Randomized
Excluded from Safety Population:			
None			**69 (100) Safety Population**
Excluded from Intent-to-Treat:			
None			**69 (100) Intent-to-Treat**
Excluded from Per-Protocol:			
121,128	Bupivacaine	Patient Had a Recurrent Hernia	
134	Levobupivacaine		
147	Bupivacaine	Received Prohibited Analgesics/Anesthetics	
004, 115, 131, 134, 136	Levobupivacaine		**60 (86.9) Per-Protocol**
1(1.44 %) Total Withdrawal[13]			**68 (98.5%) Total Completed**

[13] Patient 131 was withdrawn because of the administration of excluded medication.

Table 136. Patient Disposition

TABLE 6

LEVOBUPIVACAINE - 030721

Summary of formation of populations

by treatment group

Total population

Evaluation group	Levobupivacaine (n=35)	Bupivacaine (n=34)
Total population	35 (100.0%)	34 (100.0%)
Safety population	35 (100.0%)	34 (100.0%)
Intent-to-treat population	35 (100.0%)	34 (100.0%)
Per-protocol population	30 (85.7%)	30 (88.2%)

[Sponsor's Table 6, Item 8, Vol. 1. 83, p. 107]

Demographics

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

Table 137. Demographics - Intent–to Treat Evaluable Population

TABLE 7 LEVOBUPIVACAINE - 030721

Demographic details

by treatment group

Intent-to-treat population

Variable		Levobupivacaine (n=35)		Bupivacaine (n=34)	
Age (years)	mean	55.5		61.4	
	sd	12.2		11.4	
	minimum	28		40	
	maximum	76		88	
	n	35		34	
	missing	0		0	
Race	white	35	(100.0%)	34	(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%)
	missing	0		0	
Height (cm)	mean	174.9		177.6	
	sd	6.4		8.1	
	minimum	162		158	
	maximum	186		188	
	n	33		28	
	missing	2		6	
Weight (kg)	mean	79.69		75.77	
	sd	8.18		11.34	
	minimum	63.3		59.0	
	maximum	95.0		112.0	
	n	35		34	
	missing	0		0	

[Sponsor's Table 7, Item 8, Vol.1.83, p. 108]

"All patients in the study were white. However, there were slight differences in the distributions of age, weight and height between the treatment groups. For the intent -to-treat population, patients in the levobupivacaine group were younger on average than those in the bupivacaine group (mean in the levobupivacaine group was 55.5 years, (SD 12.2) compared to 61.4 years, (SD 11.4) in the bupivacaine group). Differences in the mean heights of each of the 2 treatment groups were smaller. In the levobupivacaine group, the mean height was 174.9 cm (SD 6.4), and that in the bupivacaine group was 177.6 cm (SD 8.1). The mean weights for the 2 treatment groups differed by almost 4 kg. The mean in the levobupivacaine group was 79.69 kg (SD 8.18), and that in the bupivacaine group was 75.77 kg (SD 11.34)."

"In the per-protocol population, the demographic trends were similar to those for the intent - to-treat population. For example, patients in the levobupivacaine group were, on average, younger (mean 56.1 years, SD 11.3 years) than those in the bupivacaine group (mean 62.5 years, SD 10.9 years)."

"In the levobupivacaine group, 27 patients (77.1%) reported 93 significant medical histories between them. A higher number, 32 patients (94.1%) in the bupivacaine group reported 110 significant medical histories. Of these, 24 patients (68.6%) in the levobupivacaine group had 61 significant medical histories that were still present and 28 patients (82.4%) in the bupivacaine group had 71 continuing significant medical histories."

"The 3 most frequently occurring body systems were 'Circulatory system', 'Digestive system' and 'Musculoskeletal system and connective tissue'. For many of the patients with medical histories under these body systems, the disease was still present. The largest difference between treatment groups was under the body system 'Digestive system', where seven patients in the levobupivacaine group (20.0%) and 11(32.4%) in the bupivacaine group reported having a significant medical/surgical history. For the majority of body systems, the treatment groups appeared to be comparable in terms of the number and percentage of patients with significant medical histories under each body system."

"Overall, there were slightly more abnormal results from the physical examination in the bupivacaine group than the levobupivacaine group. However, the differences within each body system were small, the largest difference being under the body system 'Lungs' where 3 patients (8.6%) from the levobupivacaine group and 6 from the bupivacaine group (17.6%) produced abnormal responses."

[Item 8. Vol. 1.83, p. 066 –068]

APPEARS THIS WAY
ON ORIGINAL

"For 3 body systems ('Lymph nodes', 'Anorectal' and 'Neurological'), all results from those patients examined ere found to be normal. As was to be expected, all patients in the intent-to-treat population had an abnormal .esult from physical examination of the abdomen.

For all but 4 of the body systems (namely 'Chest', 'Lungs', 'Heart' and 'Abdomen'), at least 25% of patients were not examined."

"A total of 68 patients, 35 in the levobupivacaine group and 33 in the bupivacaine, group took at least one concomitant medication before injection."

"All 35 patients (100%) in the levobupivacaine group reported taking 60 concomitant therapies between them and 33 patients (97.1%) in the bupivacaine group reported taking 75 concomitant therapies before injection."

"All but one patient (in the bupivacaine group) recorded a nervous system concomitant medication before injection. This is because the premedication midazolam fell into this category."

"The 2 most common body systems under which patients reported taking concomitant therapies were 'Alimentary tract and metabolism' and 'Cardiovascular system'. Six patients in the levobupivacaine treatment group (17.1%) and 5 (14.7%) in the bupivacaine group reported taking therapies for the 'Alimentary tract and metabolism' body system. Four patients (11.4%) in the Levobupivacaine group and 6(17.6%) in the bupivacaine group took cardiovascular system drugs."

"Many more concomitant therapies were reported to be taken after the injection. Thirty four patients (97.1%) in the levobupivacaine group reported taking 174 concomitant therapies and 31 patients (91.2%) in the bupivacaine group reported taking 135 therapies. The majority of patients who took concomitant therapies during this period took at least one drug from the 'Musculo-skeletal system'. This was because many patients took pain relief ⁻edication (eg Ibuprofen) after the injection. As for concomitant medication taken prior to the injection, the ɔcond most common body system under which patients took concomitant therapy was 'Blood and blood ıorming organs'. Nine patients (25.7%) in the levobupivacaine group and 4 (11.8%) in the bupivacaine group took such drugs."

[Item 8. Vol. 1.83, p. 069 –071]

Table 138. Medical History Details

TABLE II

Medical History Details

ICD-9 Body System Procedures In Medicine	Treatment			
	Levobupivacaine		Bupivacaine	
	N	%	N	%
Infectious and parasitic disease	1	2.9	4	11.8
Neoplasms	1	2.9	3	8.8
Endocrine, nutritional, metabolic, immunity	3	8.6	2	5.9
Blood and blood-forming organs	0	0.0	1	2.9
Mental disorders	2	5.7	1	2.9
Nervous system and sense organs	6	17.1	7	20.6
Circulatory system	9	25.7	10	29.4
Respiratory system	7	20.0	9	26.5
Digestive system	7	20.0	11	32.4
Genitourinary system	6	17.1	6	17.6
Skin and subcutaneous tissue	4	11.4	3	8.8
Musculoskeletal system and connective tissue	10	28.6	9	26.5
Congenital anomalies	0	0.0	1	2.9
Symptoms, signs and ill-defined conditions	5	14.3	8	23.5
Injury and poisoning	4	11.4	5	14.7
Examination of special symptoms	1	2.9	0	0.0

[Sponsor's Table II. Item 8. Vol. 1.83 p. 068]

SPONSOR'S EFFICACY RESULTS:

"The primary measures of efficacy were defined to be the normalised area under the VAS of post-operative pain (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)."

"Of secondary interest for the assessment of efficacy were:

- The VAS of satisfaction with the anaesthetic, measured immediately following completion of surgery.
- Global verbal rating scale of pain experienced during surgery.
- Normalised dosage of relief medication (Ibuprofen 600 mg tablets) over all available assessments (ie total dosage taken divided by the assessment time).
- Time to first dose of relief medication."

Supine VAS scores for Post-operative Pain

"The maximum mean supine VAS score was in the levobupivacaine group at the 24 h assessment (10.1 mm, SD 15.3 mm). VAS scores in both treatment groups rose sharply between the 1 h and the 3 h assessment, with patients in the levobupivacaine group reporting slightly higher scores for post-operative pain at this point than patients in the bupivacaine group (mean 8.4 mm, SD 12.1 mm compared to mean 7.2 mm, SD 10.7 mm). After this point, the scores in both treatment groups dropped in the 48 h assessment period and then rose again to the highest values between 8 and 36 h. It should be noted that at 36 and 48 h the mean VAS score was slightly lower in the levobupivacaine group."

The results for the per-protocol population show, "... differences between treatment groups in the 6-36 h assessment period. VAS scores in the levobupivacaine group were higher on average during this period than those in the bupivacaine group. However, the values at 36 h and at 48 h were similar between treatments."

The statistical analysis of this endpoint is found below, i.e., normalized supine VAS scores for post-operative pain.

[Item 8. Vol. 1. 83, p. 073 –074]

Table 139. Analysis of Primary Outcome Measurement-
Normalized Area Under Supine VAS vs. Time Curve

TABLE 16 LEVOBUPIVACAINE - 030721

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=35)	Bupivacaine (n=34)
Normalised area under curve (mm)	mean	7.86	8.01
	sd	7.77	11.19
	minimum	0.0	0.0
	maximum	34.8	43.8
	n	35	34
	missing	0	0

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

Analysis of variance test gives a treatment p-value of 1.00.

Square root transformation difference in treatment mean (adjusted for normalised dosage relief medication) is 0.002mm, corresponding 95% confidence interval for difference between treatments is (-0.71, 0.72)

[Sponsor's Table 16, Item 8, Vol. 1.83, p. 133]

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rmalized Area Under Supine VAS for Post-operative Pain vs Time Curve

The mean normalised area under the curve was slightly lower in the levobupivacaine group (7.86 mm, SD 7.77) than in the bupivacaine group (8.01 mm, SD 11.19). No statistically significant difference was detected between the treatments (p=1 .00) 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 0.002 mm. A value equal to zero would signify no treatment difference. The 95% confidence interval surrounding this estimate was (-0.71, 0.702). It should be noted that, clinically, these values are difficult to interpret as they summarise transformed data.

Rising VAS scores for Post-operative Pain

"... the rising VAS scores were higher than the supine VAS scores for both treatment groups. Again, the acute peak in the levobupivacaine group was slightly larger than that in the bupivacaine group (at 2 h, mean in levobupivacaine group was 12 mm, SD 14.6 mm and for the bupivacaine group it was 7.6 mm, SD 13.8 mm). Between 6 and 24 h, the mean VAS scores in the levobupivacaine group were noticeably higher than in the bupivacaine group, with the trend reversing for the last 2 assessments at 36 and 48 h." The per-protocol population results showed the same trends as the intent-to-treat population.

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

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

" . the mean normalised area under the curve (mm) was slightly higher in the levobupivacaine group (mean 57 mm, SD 11.68 mm) than in the bupivacaine group (mean 16.12 mm, SD 14.81mm)."

"A square root transformation and an ANOVA with terms for treatment group and normalised dosage of relief medication were used to assess treatment..." "Treatment group was non-significant at the 5% level (p=0.7 1) after adjusting for normalised dosage of relief medication. The adjusted, transformed estimate for the difference between treatments was 0.15 mm and its corresponding 95% confidence interval was (-0.65, 0.94). Again, the interpretation of these transformed estimates is complex."

"The same trend was shown in the per-protocol population as was shown for the intent-to-treat population for this variable. The difference was slightly more marked, but again quite small, with the mean in the levobupivacaine group being 17.18 mm (SD 11.97) and that in the bupivacaine group being 15.32 mm (SD 14.73)."

"For the per-protocol population, treatment group was found to be nonsignificant at the 5% level (p=0.78) after adjusting for normalised dosage of relief medication. The adjusted estimate for treatment difference on the transformed data was 0.12 mm and the corresponding 95% confidence interval was (-0.77, 1.02).

[Item 8. Vol. 1. 83, p. 074 - 076]

Table 140. Analysis of Secondary Outcome Measurement – Normalized Area Under Rising VAS vs. Time Curve

TABLE 20 LEVOBUPIVACAINE - 030721

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

by treatment group

Intent-to-treat population

Rising VAS		Levobupivacaine (n=35)	Bupivacaine (n=34)
Normalised area under curve (mm)	mean	17.57	16.12
	sd	11.68	14.81
	minimum	0.1	0.0
	maximum	48.7	54.7
	n	35	34
	missing	0	0

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

Analysis of variance test gives a treatment p-value of 0.71.

Square root transformation difference in treatment mean (adjusted for normalised dosage relief medication) is 0.15mm, corresponding 95% confidence interval for difference between treatments is (-0.65, 0.94)

[Sponsor's Tables 20, Item 8, Vol. 1.83, p.143]

Walking VAS scores for Post-operative Pain

"...the mean value for the walking VAS were not as high as those for the rising VAS, but slightly higher than those for the supine VAS for post-operative pain. The trends were similar to those for the rising VAS with mean scores in the levobupivacaine group being consistently higher than those in the bupivacaine group from 6 to 24 h, but with the trend reversing for the 36 and 48 h assessments as the levobupivacaine mean VAS scores dropped." The pattern was similar for the Per-protocol population.

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

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

"For the intent-to-treat population the mean in the levobupivacaine group was 14.41 mm (SD 11.37 mm) and that for the bupivacaine group was 12.88 mm (SD 14.10 mm)."

"...No significant difference was detected between the treatments (p=0.74 after adjusting for normalised dosage of relief medication). The adjusted estimate for the treatment difference of the transformed data was 0.131 mm. The 95% confidence interval surrounding this estimate was (-0.66, 0.92)."

"The same model was fitted for the per-protocol population as for the intent-to-treat population. Again, no statistically significant difference was found between the treatments (p=0.77) after adjusting for normalised dosage of relief medication. The adjusted estimate between treatments for the transformed data was 0.13 mm and the corresponding 95% confidence interval was (-0.73, 0.98)."

[Item 8. Vol. 1. 83, p. 077 - 078]

S of Satisfaction with the Anesthetic

"The VAS scores for satisfaction with the anaesthetic were very similar between treatment groups in the intent-to-treat population. The median [mean] in the levobupivacaine group was 95.00 [87.09]cm and that in the bupivacaine group was 95.50 [87.65]cm. It should be noted that VAS scores for satisfaction were measured only to one decimal place. However, since the number of observations in the bupivacaine group was 34, the median was taken as an average of the 17th and 18th observations."

"Wilcoxon's two-sample test produced a p-value of 0.91, which would suggest that there was no difference between treatment groups for the VAS score of satisfaction with the anaesthetic. The estimate obtained, based on Wilcoxon's two-sample test," "....was equal to 0.00 cm, and the corresponding 95% confidence interval was (-2.00 cm,3.00 cm). Hence, this again suggests that the treatment groups were equivalent in terms of VAS of satisfaction with the anaesthetic."

"In the per-protocol population, the median in the levobupivacaine group was 96.00 cm compared to a median of 96.50 cm in the bupivacaine group."

"The Wilcoxon's two-sample test produced a p-value of 0.91, which again was non-significant at the 5% level. The corresponding estimate and 95% confidence interval for treatment difference were 0.00 mm and (-3.00, 3.00 mm)."

m 8. Vol. 1. 83, p. 078]

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Table 141. Analysis of Secondary Outcome Measurement – Normalized Area Under Walking VAS vs. Time

TABLE 24 LEVOBUPIVACAINE - 030721

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=35)	Bupivacaine (n=34)
Normalised area under curve (mm)	mean	14.41	12.88
	sd	11.37	14.10
	minimum	0.1	0.0
	maximum	42.3	49.8
	n	35	34
	missing	0	0

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

Analysis of variance test gives a treatment p-value of 0.74.

Square root transformation difference in treatment mean (adjusted for normalised dosage relief medication) is 0.13mm, corresponding 95% confidence interval for difference between treatments is (-0.66, 0.92)

Table 142. Analysis of Secondary Outcome Measurement – VAS Score for Satisfaction with Anesthetic

TABLE 26 LEVOBUPIVACAINE - 030721

Summary and analysis of VAS scores for satisfaction with the anaesthetic

by treatment group

Intent-to-treat population

VAS scores (mm)		Levobupivacaine (n=35)	Bupivacaine (n=34)
VAS scores for satisfaction with anaesthetic	median	95.00	95.50
	mean	87.09	87.65
	sd	22.41	20.40
	min	0.0	1.0
	max	100.0	100.0
	n	35	34
	missing	0	0

Wilcoxon's two-sample test gives a p-value of 0.91.

Median estimate for treatment difference is 0.00 mm.
Corresponding 95% confidence intervals for the difference between treatments is (-2.00, 3.00).

[Sponsor's Tables 24 and 26, Item 8. Vol. 1.83, p. 153 and 155]

lobal Verbal Pain Rating

"For the intent-to-treat population, most patients in both treatment groups reported having 'Nil' or 'Slight' pain during surgery. Fewer patients reported having 'Moderate' pain during surgery in the levobupivacaine group (2 patients, 5.7%) than in the bupivacaine group (6 patients, 17.6%). Just one patient in each treatment group reported 'Severe' pain during surgery."

"A total of 34.3% of patients in the levobupivacaine group reported 'nil' pain compared to 41.2% of patients in the Bupivacaine group. The treatment difference for the newly classified variable in terms of 'Nil' pain recorded, was -6.9% with a 95% confidence interval of (-29.7%, 15.9%). Although no statistical difference was detected between the treatment groups (p=O.56), the 95% confidence interval was wide and therefore this analysis was inconclusive."

"...no patients eligible for the per-protocol population reported 'Severe' pain during surgery. As for the intent -to-treat population, most patients in both treatment groups in the per-protocol population reported 'Nil' or 'Slight' pain during surgery.

"The proportion of patients from the per-protocol population in the levobupivacaine group reporting 'Nil' pain was 36.7%, and that in the bupivacaine group was 43.3%, giving a difference between treatments of -6.7%. The 95% confidence interval surrounding this estimate was wide (-31.4%, 18.1%). Therefore, again, although no statistically significant difference was detected between the treatment groups (p=0.60), the analysis was inconclusive and larger differences cannot be ruled out."

The statistical reviewer has performed an alternate statistical test of the endpoint, however, the results of the two ifferent analyses are similar, i.e., no statistically significant differences were found

tem 8. Vol. 1. 83, p. 079]

Table 143. Analysis of Secondary Outcome Measurement – Global Verbal Rating Scale

TABLE 28 LEVOBUPIVACAINE - 030721

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=35)		Bupivacaine (n=34)	
Global verbal rating scale of pain experienced during surgery	Nil	12	(34.3%)	14	(41.2%)
	Slight	20	(57.1%)	13	(38.2%)
	Moderate	2	(5.7%)	6	(17.6%)
	Severe	1	(2.9%)	1	(2.9%)
	Missing	0		0	

Comparing 'Nil' pain vs 'Slight', 'Moderate' or 'Severe' pain, fitting the logit model gives a p-value of 0.56.

Observed percentage difference between treatments is -6.9%.
95% confidence interval for percentage difference between treatments is (-29.7%, 15.9%).

[Sponsor's Table 28, Item 8, Vol. 1.83, p. 158]

elief Medication

Normalized Dosage of Relief Medication

"Slightly more mg/hr of relief medication were taken by patients in the levobupivacaine group than in the bupivacaine group. The median in the levobupivacaine group was 54.899 mg/hr compared to 48.520 mg/hr in the bupivacaine group."

"Wilcoxon's two-sample test produced a p-value equal to 0.11. This p-value was smaller than those for other analyses which suggests that for this variable there may be a relationship with treatment group (in line with the per-protocol analysis results below). However, it was not significant at the 5% level. The 95% confidence interval surrounding this estimate was calculated as (-0.462, *25.255*)."

"There was a greater difference between treatment groups for patients in the per-protocol population in terms of the normalised dosage of relief medication. The median in the levobupivacaine group was 63.003 mg/h compared to 43.450 mg/h in the bupivacaine group."

"Wilcoxon's two-sample test performed on data from the per-protocol population produced a p-value that was significant at the 5% level (p=0.041). Hence, there is evidence to suggest that for the per-protocol population, patients in the levobupivacaine group took more medication over the normalising time than patients in the bupivacaine group. The estimate of median treatment difference was equal to 12.875 and the corresponding 95% confidence interval was (0.000, 26.993)."

.em 8. Vol. 1. 83, p. 080 -081]

Time to First Dose of Relief Medication

"There were 5 censored observations (ie patients who did not take any relief medication up to and including the 48 h assessment). One of these was in the levobupivacaine group and the remaining 4 were in the bupivacaine group. The results with and without the inclusion of censored observations were similar, but it can be seen that the removal of the censored observations slightly reduced the median time to first dose in the bupivacaine group. The median [mean] time to first dose for patients the levobupivacaine group was 9.50 [mean values not provided by sponsor] h with the inclusion of the censored observation, and 9.33 h with this value excluded. In the Bupivacaine group, the median including censored observations was 9.58 h, but without was 9.10 h."

"A log rank test performed on these data to compare the results between treatment groups, including censored observations, produced a p-value of 0.385, suggesting that there was no difference between treatment groups in terms of time to first dose of relief medication.

"The results for the per-protocol population were very similar to those for the intent-to-treat population. The p-value resulting from the log-rank test on these data was 0.191, which was non-significant at the 5% level."

The statistical reviewer has performed an additional test of the proportion of censored patients with respect to the time to first dose of relief medication and also found no statistically significant differences between treatment groups.

.em 8. Vol. 1. 83, p. 081 - 082]

Table 144. Analysis of Secondary Outcome Measurements - Normalized Dosage of Relief

TABLE 30

LEVOBUPIVACAINE - 030721

Summary and analysis of normalised dosage of relief medication

by treatment group

Intent-to-treat population

Normalised dosage		Levobupivacaine (n=35)	Bupivacaine (n=34)
Normalised dosage of relief medication (mg/hr)	median	54.899	48.520
	mean	52.801	43.218
	sd	25.800	27.662
	min	0.00	0.00
	max	88.83	110.02
	n	35	34
	missing	0	0

Wilcoxon's two-sample test gives a p-value of 0.11.

Median estimate for treatment difference is 12.210 mg/hr.
Corresponding 95% confidence interval for the difference between treatments is (-0.462, 25.255).

[Sponsor's Table 30, Item 8, Vol. 1.83, p. 160]

Table 145. Analysis of Secondary Outcome Measurements – Time to First Dose of Relief Medication

TABLE 32

LEVOBUPIVACAINE - 030721

Summary and analysis of time to first dose of relief medication

by treatment group

Intent-to-treat population

Relief medication		Levobupivacaine (n=35)	Bupivacaine (n=34)
Time (hrs) to first dose (including censored patients)	25th percentile	5.80	4.28
	median	9.50	9.58
	75th percentile	12.27	13.08
	interquartile range	6.5	8.8
	n	35	34
	missing	0	0
Censored patients	uncensored observations	34 (97.1%)	30 (88.2%)
	censored observations	1 (2.9%)	4 (11.8%)
	missing	0	0
Time (hrs) to first dose (not including censored patients)	25th percentile	5.80	3.23
	median	9.33	9.10
	75th percentile	12.08	12.67
	interquartile range	6.3	9.4
	n	34	30
	missing	0	0

N.B. The time of the 48 Hour assessment was used as the time of study completion for censored observations.

Log-rank test for difference between treatments in time to first dose (including censored observations) gives a p-value of 0.385.

[Sponsor's Table 32 Item 8, Vol. 1.83, p. 162]

REVIEWER'S EFFICACY DISCUSSION

No significant differences were found between treatment groups for the primary efficacy variable - VAS for post-operative pain. No significant differences were found between treatment groups for all of the secondary efficacy variables, with the exception of the per-protocol levobupivacaine population who took more ibuprofen after surgery than their counterparts on bupivacaine (p=0.041).

The clinical data has demonstrated that levobupivacaine is effective when administered for an inguinal hernia nerve block following inguinal hernia repair. This conclusion is based upon the evidence that patients received some level of analgesia sufficient for inguinal hernia repair. However, there has been no evidence to show that they are different.

STUDY # 006154

PROTOCOL SYNOPSIS:

Title: "A Randomized Multicentre, Double-blind, Parallel Group Study to Evaluate the Dose Response, Kinetics and Safety of 0.25% and 0.5% Levobupivacaine (S-enantiomer) with 0.5% Bupivacaine (racemic mixture) in Patients Undergoing Elective Surgery Under Brachial Plexus Block"

Primary Objective: "To compare the efficacy (duration and onset of anesthesia) of two different concentrations of levobupivacaine (0.25% and 0.5%) with 0.5% racemic bupivacaine."

Secondary Objective: "To determine the plasma concentrations and safety profiles of levobupivacaine (0.25% and 0.5%) and 0.5% racemic bupivacaine."

[item 8, Vol. 1.85, p. 011]

Study Design:

The study is designed as a randomized, double-blind, 3 limb parallel group comparative study of the efficacy, safety and pharmacokinetics of 0.25% levobupivacaine 0.5% levobupivacaine and 0.5% bupivacaine in patients undergoing elective surgery under supraclavicular brachial plexus block. The protocol calls for a total of seventy-six patients to be randomized to three treatment arms.

Group I	0.25% levobupivacaine (0.4 ml/kg)
Group II	0.5% levobupivacaine (0.4 ml/kg)
Group III	0.5% bupivacaine (0.4 ml/kg)

Eligible patients will be ASA Class I - III males or females $\geq$ 18 years of age, consenting to receive supraclavicular brachial plexus block for uncomplicated hand surgery. Patients must have no prior history of systemic illness, presence of infection at the anesthetic site, drug or alcohol abuse within the previous 6 months, or not participated in another clinical trial in the previous 23 months. Women of childbearing potential must not be pregnant or lactating and must be using adequate contraceptive method.

Prior to surgery, eligible patients underwent a brief screening phase followed by a 1:1:1 randomization to receive a brachial plexus block using either 0.25% levobupivacaine, 0.5% levobupivacaine or 0.5% bupivacaine for uncomplicated hand surgery. Sixty minutes prior to entering the operating room, patients received 10-20 mg of temazepam, orally.

The brachial plexus block was identified via a peripheral nerve stimulator at 0.4 mA. After confirming a negative aspiration, 0.4 ml/kg of randomized drug was given over 60 seconds, with aspiration after every 5 – 10 ml. Completion of the drug administration was defined as Time 0. Surgery began thirty minutes later.

In the event of an intravascular injection or if pneumothorax was suspected, the patient was withdrawn and supportive measures were instituted. If a poor block was assessed, general anesthesia was induced using propofol and fentanyl.

A propofol infusion (3-4 mg/kg/hr) was provided for intraoperative sedation.

Sensory block was assessed using the blunt end of a 27 gauge dental needle at 2, 5, 10, 15, 20, 25 and 30 minutes post-dose and then every 30 minutes until complete reversal of the block.

lotor block was assessed using the following scale:

- 0 = no paralysis
- 1 = difficulty in raising shoulder and weakness of hand
- 2 = inability to move upper limb

This assessment was made at 2, 5, 10, 15, 20 25, and 30 min post-dose and then every 30 min until return of full motor power.

An overall assessment of the quality of block was made during the operation by the anesthesiologist and surgeon using the following criteria:

- 0 = failure
- 1 = unsatisfactory
  - (i) inadequate analgesia
  - (ii) inadequate relaxation
  - (iii) patient requires general anesthesia
- 2 = complete block

Pharmacokinetic sampling was performed from 31 patients at pre-dose, 0, 10, 20, 30, 45, 60 min and 1.5, 2, 4, 6, 8, 10, and 24 hours post-dose.

STATISTICAL ANALYSIS

The primary efficacy response variable was defined as the duration of block using the intent-to-treat population. The duration of block was redefined (at the request of the sponsor after the study blindness was broken – seen in italics) as follows:

"Duration of sensory block was redefined as time to onset of block (ie when the first analgesia to pinprick was detected) until complete return of sensory touch (ie time when painful sensation returned in all dermatomes), *irrespective of whether or not a general anaesthetic was given.*"

"Duration of motor block was redefined as time to onset of block until complete return of motor power, *irrespective of whether or not a general anaesthetic was given.*"

"In the event of an intervention (*eg* use of general anaesthetic for a poor block) the duration of block was recorded as the time from onset of sensory block to the time to intervention. Those patients who did not attain a block have been excluded from the statistical analysis. The duration of block was analysed using analysis of variance techniques (ANOVA) with terms for treatment, centre and treatment by centre interaction. Using the error variance from the ANOVA, pairwise comparisons of the three treatments were made using Student's 't'-tests. To compensate for multiple comparisons, a sequentially rejective Bonferroni-Holm method was used. Estimates of treatment differences and the associated 95% confidence intervals were calculated."

"The secondary efficacy response variables were defined as follows:

Time to onset of sensory block ie time between end of drug administration and time when first analgesia to pinprick was detected. Time to onset of, and duration of motor block ie time between end of drug administration and time when first loss of motor power was detected and time between first recorded loss of motor power to complete return of motor power."

"Both these variables were analysed using ANOVA methods as described above.
For the overall assessment of the quality of block, scores of O (failure) and 1 (unsatisfactory or partial block) were considered *treatment failures* and a score of 2
(complete block) as a *treatment success.* This derived endpoint was analysed using
logistic regression."

"All analyses were performed using both 'per-protocol' and 'intent-to-treat' populations."

[Item 8, Vol. 1.85, p. 025 –026]

"At the request of the Sponsor, the following additional endpoints were statistically analysed for the 'intent-to-treat' population only:

1. Time to onset and duration of block at each dermatome. Time to onset and time to return of sensation in each dermatome (offset time) were calculated for each dermatome separately. In the case of 'patchy' blocks, onset and offset times were assigned by the investigator. Duration of block was taken as the time from the onset time until the offset time. Time to onset and duration of sensory block have been illustrated graphically using treatment group medians and their respective interquartile range.

2. Time to onset and duration of each grade of motor block. Time to onset and duration of motor block have been illustrated graphically using treatment group medians and their respective interquartile range."

"In the event of a general anaesthetic being used before onset of block, the patient was excluded from the analysis. All the above additional endpoints were analysed using a Kruskal-Wallis non-parametric analysis of variance. Pairwise comparisons between treatments were performed using a 'Z'-test based on rank sums. To compensate for multiple comparisons, a sequentially rejective Bonferroni-Holm method was used. Treatment group medians have been presented together with the range, the p-value for the 'Z'-test and significance level of the 'Z'-test using a sequentially rejective Bonferroni-Holm method. For the purposes of these analyses, data from all centres were combined (ie. no account was taken of any possible centre effect)."

"In addition to these analyses, the proportion of patients responding at each dermatome and each grade of motor block were compared between treatment groups using a chi-squared test."

[Item 8. Vol. 1.85, p.026 027]

PROTOCOL AMENDMENT:

The following amendments were dated 2/24/95, 7/11/95 and 6/3/96. They consist of following changes:

1. Monitoring
   - Heart rate, Systolic and Diastolic Mean Arterial Pressure - The sponsor has added additional assessment times as follows: "Between 30 minutes and 5 hours, assessments will be made every 30 minutes. After 5 hours assessments will be made hourly."
   - "Sensory block will be assessed every 30 minutes until complete regression of the block" – this statement has been added to clarify the time period between assessments post-block.
   - Motor block - The sponsor has added additional assessment times as follows: "Between 30 minutes and 5 hours, assessments will be made every 30 minutes. After 5 hours assessments will be made hourly."

2. Pharmacokinetics
   - The sponsor has changed the quantity of blood samples to be drawn from 5 to 6ml.
   - The sponsor will centrifuge blood at room temperature and store it at -20^0 C or -70^0 C due to difficulties in obtaining refrigerated centrifuges.

3. Statistical Analysis (See full description of statistical analysis in Section 4. 2. 13. 2 "Statistical Analysis, p. 291)
   - At the request of the sponsor, after the blindness of the study had been broken, the duration of sensory and motor blocks was changed to account for the event of a general anesthetic, i.e., the time to onset and offset of sensory block would remain the same irrespective or whether or not a general anesthetic had been induced.
   - The sponsor has added time points to include the time to onset and duration of sensory and motor block at each dermatome as well as the planned analysis, i.e., Krukal-Wallis nonparametric analysis of variance.
   - All vital sign parameters will be analyzed using ANOVA.

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 76 patients randomized, 75 (98.7%) received study medication. Patient 069 (0.25% levobupivacaine) was withdrawn prior to dosing due to of complaints of chest pain during needle localization.

Of the 75 patients who received the study drug, one patient (Patient # 006 – 0.5% bupivacaine) was withdrawn secondary to suspected intravenous administration of study medication. Therefore, of the 76 patients randomized, 74 (97.4%) were evaluated for Intent-to-Treat.

Ten patients were excluded from the per-protocol population - 5 patients from the 0.25% levobupivacaine group, 4 patients from the 0.5% levobupivacaine, and 1 patient from the bupivacaine group. Therefore, the total per-protocol population was 64 (84.2%).

The majority of per-protocol violations occurred secondary to patients receiving prohibited medications. However, one patient (Patient 055 – experienced a ring block at 30 min, i.e., inadequate anesthesia).

Table 146. Analysis of Protocol Violations

TABLE L1.1

Efficacy Evaluation Population

STUDY ENROLMENT/EVALUATION	0.25% LEVOBUPIVACAINE	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE	TOTAL
Total Enroled	26	26	24	76
Patients withdrawn prior to dosing	1	0	0	1
Total Dosed	25	26	24	75
Patients eliminated from intent-to-treat analysis	0	0	1	0
Total evaluated for intent-to-treat analysis	25	26	23	74
Patients eliminated from the per-protocol analysis	5	4	1	10
Total evaluated for per-protocol analysis	20	22	22	64

Table 147. Patient - Specific Protocol Violations

TABLE L1.2

Efficacy Evaluation Populations
Patients Excluded from Intent-to-Treat and Per-Protocol Analysis

Patient	Treatment	Patients withdrawn prior to dosing
069	1	Chest pain during attempted needle localisation
		Patients excluded from intent-to-treat population
006	3	Likely iv administration
		Patients excluded from per-protocol population
020	3	Alfentanil, ketolorac administration
022	1	Alfentanil, droperidol, nitrous oxide general anaesthetic
027	1	Midazolam
029	2	Alfentanil (not general anaesthetic)
036	1	Alfentanil, nitrous oxide general anaesthetic
055	2	Ring block at 30 min
057	1	Nitrous oxide general anaesthetic
064	2	Midazolam at 35 min
066	1	GA - Alfentanil
067	2	GA - Alfentanil, nitrous oxide

Key for Treatment

1 = 0.25% Levobupivacaine
2 = 0.5% Levobupivacaine
3 = 0.5% Bupivacaine

[Sponsor's Tables, L1.1 and L1.2 Item 8, Vol. 1.85, p. 310 and 311]

Demographics

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

Table 148. Demographics - Intent–to Treat Evaluable Population

TABLE K1.1.2

Demographic Data
Summary Statistics: Intent-to-Treat Population

		Treatment			
		0.25% LEVOBUPIVACAINE	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE	All Patients
Age (Years)	Mean	52.68	55.85	55.04	54.53
	SD	14.55	13.49	18.77	15.49
	Min	19.0	25.0	26.0	19.0
	Max	84.0	75.0	81.0	84.0
	N	25	26	23	74
Height (cm)	Mean	170.92	170.85	166.65	169.57
	SD	11.79	10.71	8.64	10.55
	Min	151.0	153.0	150.0	150.0
	Max	193.0	193.0	182.0	193.0
	N	25	26	23	74
Weight (kg)	Mean	72.24	72.47	67.81	70.95
	SD	12.32	15.17	13.97	13.86
	Min	48.0	38.0	48.5	38.0
	Max	95.0	100.0	98.0	100.0
	N	25	26	23	74
MALE	N	15	19	14	48
FEMALE	N	10	7	9	26

[Sponsor's Table K1.1.2., Item 8, Vol.1.835, p. 186]

SPONSOR'S EFFICACY RESULTS:

Time to Onset and Duration of Block

Sensory Block: Intent-to-Treat Population

"The number (%) of patients not attaining a block were 0 (0%), one (4%) and one (4%) for 0.25% levobupivacaine, 0.5% levobupivacaine and 0.5% bupivacaine respectively. All patients who did not attain a sensory block were excluded from the statistical analysis."

"There were no statistically significant differences between the three treatments in terms of mean revised duration of sensory block or time to onset of sensory block."

"Duration of sensory block was found, on average, to be statistically significantly longer for the 0.5% levobupivacaine treated group compared with the 0.25% levobupivacaine group."

Motor Block: Intent-to-Treat Population

"The number (%) of patients not attaining a motor block were 0 (0%), 2 (8%) and 2 (9%) for 0.25% levobupivacaine, 0.5% levobupivacaine and 0.5% bupivacaine respectively. All patients who did not attain a motor block were excluded from the corresponding analysis."

"There were no statistically significant differences between the 3 treatments in terms of mean duration, revised duration (adjusted p=0.026)and time to onset of motor block."

[Item 8, Vol. 1.85, p. 039 – 040]

Table 149. Analysis of Primary Efficacy Variable – Duration of Sensory Block

TABLE M1.1.1

Duration of Sensory Block (min)
Intent-to-treat Population: Excluding Patients Not Attaining Block
Statistical Analysis

	TREATMENT		
	0.25% LEVOBUPIVACAINE	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
NUMBER OF PATIENTS	25	24	22
ADJUSTED MEAN (MIN)	666.9	1014.8	854.0

COMPARISON	ESTIMATE OF DIFFERENCE (MIN)	LOWER 95% CONFIDENCE INTERVAL (MIN)	UPPER 95% CONFIDENCE INTERVAL (MIN)	P-VALUE[1] (SL)
0.5% BUPIVACAINE - 0.25% LEVOBUPIVACAINE	187.1	-60.1	434.4	0.14 (NS)
0.5% BUPIVACAINE - 0.5% LEVOBUPIVACAINE	-160.7	-407.3	85.8	0.20 (NS)
0.5% LEVOBUPIVACAINE - 0.25% LEVOBUPIVACAINE	347.9	113.2	582.5	0.004 (*)
SIGNIFICANCE LEVEL OF TREATMENT EFFECT[2]				0.016
SIGNIFICANCE LEVEL OF CENTRE EFFECT[2]				0.90
SIGNIFICANCE LEVEL OF TREATMENT x CENTRE INTERACTION[2]				0.53

(1) P-value of 't'-test using residual error from ANOVA
(2) P-value of F-test from ANOVA

SL Significance level of 't'-test using a sequentially rejective Bonferroni-Holm Method
* Statistically significant at the 5% level using a sequentially rejective Bonferroni-Holm Method
NS Not statistically significant at the 5% level using a sequentially rejective Bonferroni-Holm Method

Note: Patients not attaining block includes those where intervention occurred prior to block onset
Patient 046 excluded from analysis as assessment of block was not recorded prior to surgery

Duration is taken as the time from onset of block until complete return of sensory touch except where a general anaesthetic was given. In the event of such an intervention, duration is taken as time from onset of block until intervention (as defined before the study blindness was broken)

[Sponsor's Table M1.1.1, Item 8 Vol. 1.85, p. 367]

Table 150. Revised[14] Analysis of Primary Efficacy Variable- Duration of Sensory Block

[illegible] to Onset of Motor Block

TABLE M1.1.2

Revised Duration of Sensory Block (min)
Intent-to-treat Population: Excluding Patients Not Attaining Block
Statistical Analysis

	TREATMENT		
	0.25% LEVOBUPIVACAINE	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
NUMBER OF PATIENTS	25	24	22
ADJUSTED MEAN (MIN)	896.3	1027.4	912.7

COMPARISON	ESTIMATE OF DIFFERENCE (MIN)	LOWER 95% CONFIDENCE INTERVAL (MIN)	UPPER 95% CONFIDENCE INTERVAL (MIN)	P-VALUE[1] (SL)
0.5% BUPIVACAINE - 0.25% LEVOBUPIVACAINE	16.4	-160.9	193.6	0.85 (NS)
0.5% BUPIVACAINE - 0.5% LEVOBUPIVACAINE	-114.7	-291.4	62.0	0.20 (NS)
0.5% LEVOBUPIVACAINE - 0.25% LEVOBUPIVACAINE	131.1	-37.1	299.3	0.12 (NS)
SIGNIFICANCE LEVEL OF TREATMENT EFFECT[2]				0.25
SIGNIFICANCE LEVEL OF CENTRE EFFECT[2]				0.93
SIGNIFICANCE LEVEL OF TREATMENT X CENTRE INTERACTION[2]				0.38

(1) P-value of 't'-test using residual error from ANOVA
(2) P-value of F-test from ANOVA

SL Significance level of 't'-test using a sequentially rejective Bonferroni-Holm Method
NS Not statistically significant at the 5% level using a sequentially rejective Bonferroni-Holm Method

Note: Patients not attaining block includes those where intervention occurred prior to block onset
Patient 046 excluded from analysis as assessment of block was not recorded prior to surgery

Duration is taken as time from onset of block until complete return of sensory touch irrespective of any intervention (as defined after the study blindness was broken)

[Sponsor's Table M1.1.2, "Revised Duration of Sensory Block", Item 8 , Vol. 1.85, p. 368]

[14] Revised- Sensory and motor block duration were redefined in the revised statistical methods as the time of onset to the complete return of sensation or motor power *irrespective of whether a general anesthetic was given or not* – italicized segment of sentence represents the revision.

Sensory Block: Per-Protocol Population

"All patients in the 'per-protocol' population attained a sensory block. There were no statistically significant differences between the three treatments in terms of either mean duration, revised duration or time to onset of sensory block."

Motor Block: Per-Protocol Population

"The number (%) of patients not attaining a motor block were 0 (0%), 0 (0%) and one (5%) for 0.25% levobupivacaine, 0.5% levobupivacaine and 0.5% bupivacaine respectively. All patients who did not attain a motor block were excluded from the corresponding analysis."

"There was no statistically significant differences between the 3 treatments in terms of mean duration, revised duration and time to onset of motor block."

Overall Assessment of Block

"There was no evidence of a statistically significant difference in the success rates between treatment for either population"

Time to Onset and Duration of Sensory Block at Each Dermatome

"Time to onset and duration of sensory block were calculated for each dermatome. Patients who did not attain a block were excluded from the analyses."

"There was no evidence of any statistically significant differences in time to onset or duration of block between the 3 treatments for any of the dermatomes."

[Item 8, Vol.1.85, p. 041-045]

Time to Onset and Duration of Each Grade of Motor Block

"Time to onset and duration of block were calculated for each grade of motor block. For the purposes of the statistical analysis and summary tables, only patients attaining the grade of interest were considered. "

"There was no evidence of any statistically significant differences in time to onset of block between the three treatments for grades 1 and 2."

"On average, duration of grade 1 motor block was statistically significantly longer for those patients who received 0.5% levobupivacaine compared with 0.25% levobupivacaine There were no other statistically significant differences between treatments in duration of grade 1 motor block."

"There was no evidence of any statistically significant differences in duration of grade 2 motor block between the 3 treatments."

Number of Patients Responding at Each Dermatome

"There was no evidence of a statistically significant difference in response rates between the three treatment groups for any dermatome."

Number of Patients Responding at Each Grade of Motor Block

"There was no evidence of a significant difference in response rates between the three treatment groups for each grade of motor block."

"There were no statistically significant differences between the 3 treatments in terms of mean duration, revised duration and time to onset of motor block."

[Item 8, Vol. 1.85, p. 045-046]

Table 151. Analysis of Secondary Efficacy Variable – Time to Onset of Sensory Block

TABLE M1.1.3

Time to Onset of Sensory Block (min)
Intent-to-treat Population: Excluding Patients Not Attaining Block
Statistical Analysis

	TREATMENT		
	0.25% LEVOBUPIVACAINE	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
NUMBER OF PATIENTS	25	24	22
ADJUSTED MEAN (MIN)	6.4	5.5	7.4

COMPARISON	ESTIMATE OF DIFFERENCE (MIN)	LOWER 95% CONFIDENCE INTERVAL (MIN)	UPPER 95% CONFIDENCE INTERVAL (MIN)	P-VALUE[1] (SL)
0.5% BUPIVACAINE - 0.25% LEVOBUPIVACAINE	1.1	-2.6	4.7	0.57 (NS)
0.5% BUPIVACAINE - 0.5% LEVOBUPIVACAINE	2.0	-1.6	5.6	0.28 (NS)
0.5% LEVOBUPIVACAINE - 0.25% LEVOBUPIVACAINE	-0.9	-4.4	2.5	0.59 (NS)
SIGNIFICANCE LEVEL OF TREATMENT EFFECT[2]				0.55
SIGNIFICANCE LEVEL OF CENTRE EFFECT[2]				0.010
SIGNIFICANCE LEVEL OF TREATMENT x CENTRE INTERACTION[2]				0.98

(1) P-value of 't'-test using residual error from ANOVA
(2) P-value of F-test from ANOVA

SL Significance level of 't'-test using a sequentially rejective Bonferroni-Holm Method
NS Not statistically significant at the 5% level using a sequentially rejective Bonferroni-Holm Method

Note: Patients not attaining block includes those where intervention occurred prior to block onset
Patient 046 excluded from analysis as assessment of block was not recorded prior to surgery

[Sponsor's Table M1.1.3, "Time to Onset of Sensory Block", Item 8, Vol. 1.85, p.369]

Table 152. Analysis of Secondary Efficacy Variable – Duration of Motor Block

TABLE M1.1.4

Duration of Motor Block (min)
Intent-to-treat Population: Excluding Patients Not Attaining Block
Statistical Analysis

	TREATMENT		
	0.25% LEVOBUPIVACAINE	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
NUMBER OF PATIENTS	25	24	21
ADJUSTED MEAN (MIN)	638.1	1037.0	895.7

COMPARISON	ESTIMATE OF DIFFERENCE (MIN)	LOWER 95% CONFIDENCE INTERVAL (MIN)	UPPER 95% CONFIDENCE INTERVAL (MIN)	P-VALUE[1] (SL)
0.5% BUPIVACAINE - 0.25% LEVOBUPIVACAINE	257.6	17.9	497.4	0.036 (NS)
0.5% BUPIVACAINE - 0.5% LEVOBUPIVACAINE	-141.3	-382.3	99.6	0.25 (NS)
0.5% LEVOBUPIVACAINE - 0.25% LEVOBUPIVACAINE	399.0	176.2	621.8	<0.001 (*)
SIGNIFICANCE LEVEL OF TREATMENT EFFECT[2]				0.003
SIGNIFICANCE LEVEL OF CENTRE EFFECT[2]				0.65
SIGNIFICANCE LEVEL OF TREATMENT x CENTRE INTERACTION[2]				0.45

(1) P-value of 't'-test using residual error from ANOVA
(2) P-value of F-test from ANOVA

SL Significance level of 't'-test using a sequentially rejective Bonferroni-Holm Method
* Statistically significant at the 5% level using a sequentially rejective Bonferroni-Holm Method
NS Not statistically significant at the 5% level using a sequentially rejective Bonferroni-Holm Method

Note: Patients not attaining block includes those where intervention occurred prior to block onset

Duration is taken as the time from onset of block until complete return of motor power except where a general anaesthetic was given. In the event of such an intervention, duration is taken as time from onset of block until intervention (as defined before the study blindness was broken)

[Sponsor's Table M1.1.4, "Duration of Motor Block", Item 8, Vol. 1.85, p. 370]

Table 153. Analysis of Secondary Efficacy Variable – Revised Duration of Motor Block

TABLE M1.1.5

Revised Duration of Motor Block (min)
Intent-to-treat Population: Excluding Patients Not Attaining Block
Statistical Analysis

	TREATMENT		
	0.25% LEVOBUPIVACAINE	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
NUMBER OF PATIENTS	25	24	21
ADJUSTED MEAN (MIN)	848.5	1037.0	952.1

COMPARISON	ESTIMATE OF DIFFERENCE (MIN)	LOWER 95% CONFIDENCE INTERVAL (MIN)	UPPER 95% CONFIDENCE INTERVAL (MIN)	P-VALUE[1] (SL)
0.5% BUPIVACAINE - 0.25% LEVOBUPIVACAINE	103.6	-74.4	281.6	0.25 (NS)
0.5% BUPIVACAINE - 0.5% LEVOBUPIVACAINE	-84.9	-263.8	94.0	0.35 (NS)
0.5% LEVOBUPIVACAINE - 0.25% LEVOBUPIVACAINE	188.5	23.1	353.9	0.026 (NS)
SIGNIFICANCE LEVEL OF TREATMENT EFFECT[2]				0.082
SIGNIFICANCE LEVEL OF CENTRE EFFECT[2]				0.99
SIGNIFICANCE LEVEL OF TREATMENT x CENTRE INTERACTION[2]				0.55

(1) P-value of 't'-test using residual error from ANOVA
(2) P-value of F-test from ANOVA

SL Significance level of 't'-test using a sequentially rejective Bonferroni-Holm Method
NS Not statistically significant at the 5% level using a sequentially rejective Bonferroni-Holm Method

Note: Patients not attaining block includes those where intervention occurred prior to block onset

Duration is taken as time from onset of block until complete return of motor power irrespective of any intervention (as defined after the study blindness was broken)

[Sponsor's Table M1.1.5, "Revised Duration of Motor Block", Item 8, Vol. 1.85, p.371]

Table 154. Analysis of Secondary Efficacy Variable – Time to Onset of Motor Block

TABLE M1.1.6

Time to Onset of Motor Block (min)
Intent-to-treat Population: Excluding Patients Not Attaining Block
Statistical Analysis

	TREATMENT		
	0.25% LEVOBUPIVACAINE	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
NUMBER OF PATIENTS	25	24	21
ADJUSTED MEAN (MIN)	10.2	5.6	6.4

COMPARISON	ESTIMATE OF DIFFERENCE (MIN)	LOWER 95% CONFIDENCE INTERVAL (MIN)	UPPER 95% CONFIDENCE INTERVAL (MIN)	P-VALUE[1] (SL)
0.5% BUPIVACAINE - 0.25% LEVOBUPIVACAINE	-3.9	-10.8	3.1	0.27 (NS)
0.5% BUPIVACAINE - 0.5% LEVOBUPIVACAINE	0.7	-6.3	7.8	0.84 (NS)
0.5% LEVOBUPIVACAINE - 0.25% LEVOBUPIVACAINE	-4.6	-11.1	1.9	0.16 (NS)
SIGNIFICANCE LEVEL OF TREATMENT EFFECT[2]				0.33
SIGNIFICANCE LEVEL OF CENTRE EFFECT[2]				0.090
SIGNIFICANCE LEVEL OF TREATMENT x CENTRE INTERACTION[2]				0.35

(1) P-value of 't'-test using residual error from ANOVA
(2) P-value of F-test from ANOVA

SL Significance level of 't'-test using a sequentially rejective Bonferroni-Holm Method
NS Not statistically significant at the 5% level using a sequentially rejective Bonferroni-Holm Method

Note: Patients not attaining block includes those where intervention occurred prior to block onset

[Sponsor's Table M1.1.6, "Time to Onset of Motor Block", Item 8, Vol. 1.85, p.372]

REVIEWER'S EFFICACY DISCUSSION

The primary efficacy measure - duration of sensory block in the intent to treat population and the secondary efficacy measure - motor block duration in the intent-to-treat population – were both found to be statistically significantly longer for the 0.5% levobupivacaine group than the 0.25% levobupivacaine group.

The duration of grade 1 motor block was statistically significantly longer for the 0.5% levobupivacaine group compared with the 0.25% levobupivacaine group.

The clinical data has demonstrated that levobupivacaine is (1) effective when administered as an supraclavicular brachial plexus block and, (2) demonstrates a concentration effect, i.e. increased concentration results in a longer duration of effect. This conclusion is based upon the evidence that patients received some level of analgesia sufficient for hand surgery.

STUDY # 030543

PROTOCOL SYNOPSIS:

Title: "A Study to Compare the Efficacy and Safety of 0.75% Levobupivacaine with 0.75% Bupivacaine in Peribulbar Block for Ophthalmic Anterior Segment Surgery

Primary Objective: "The efficacy of 0.75% levobupivacaine was compared with 0.75% bupivacaine in peribulbar block."

Secondary Objective: "The relative safety profiles of the 2 different formulations were compared."

[Item 8, Vol. 1.87, p. 016]

Study Design:

ne study is designed as a single center, randomized, double-blind, parallel group comparative study of the efficacy, and safety of 0.75% levobupivacaine with 0.75% racemic bupivacaine in peribulbar block for ophthalmic anterior segment surgery. The protocol calls for two groups of twenty-five patients to each be randomly assigned to one of two treatment arms.

Group I	0.75% levobupivacaine with 7.5 iu.ml $^{-1}$ hyaluronidase
Group II	0.75% bupivacaine with 7.5 iu.ml $^{-1}$ hyaluronidase

Eligible patients were ASA Class I or II males $\geq$ 18 years of age, consenting to receive peribulbar block for ophthalmic anterior segment surgery. Patients had no prior history of systemic illness, drug or alcohol abuse within the previous 6 months, participation in this or some other clinical trial in previous month, severe visual handicap in the other eye. Women of child-bearing potential must not be pregnant or lactating and must be using an adequate form of contraception.

Eligible patients underwent a brief screening phase followed by a 1:1 randomization (25 patients per group) to receive either 0.75% levobupivacaine or 0.75% bupivacaine via peribulbar block. All patients also received (1) 7.5 iu.ml $^{-1}$ hyaluronidase with the study medication, (2) mydriatic drops to dilate the pupils and, (3) 0.4% Benoxinate drops for conjunctival anesthesia. After 2 min, with the patient in primary gaze position, a 1.5 ml injection of lidocaine solution was injected followed in 2 min by 5 mls of study solution. Thereafter, serial injections of study solution were made in 5 min intervals. If after the third injection of study drug, inadequate block was achieved, the patient was withdrawn from the study. The total volume of anesthesia required to achieve the block was recorded.

Patients received a total of 3–5 ml (22.5-37.5 mg) of randomized study solution depending upon the size (volume capacity) of their globes.

. ne primary measure of efficacy was defined as the time to anesthesia suitable for surgery, i.e., akinesia score of at least 18. The akinesia scoring system was used to assess degree of anesthesia for the 4 recti muscles, orbicularis oculi and levator palpebrae superioris according to the following scale:

Akinesia Scoring System:

0 = full movement
1 = almost full movement
2 = partial movement
3 = no movement

Assessments were made at pre-dose, 2, 4, 6, 8, 10, 15, 20, 25, and 30 min following the first injection or until satisfactory block was obtained. This assessment was repeated at the follow-up visit 24 hours post-discharge in order to confirm regression (score of less than 18) of the block.

The patient assessed peri-operative analgesia immediately after the administration of the block and immediately after surgery using the following 3 point scale:

Perioperative Analgesia Scoring System

0 = No pain
1 = Some pain
2 = Much pain

The surgeon rated the operating conditions according to the amount of eye movement present during surgery, where 0 = no movement, 1 = minimal movement, and 2 = excessive movement.

Table 155. Schedule of Assessments

TABLE I

Schedule of Assessments - Study Number: ICR 030543

Assessment	Timepoint																
	Previously	Immediately prior to Pertubator Injection	Pertubator Injection	2 min	4 min	6 min	8 min	10 min	15 min	20 min	25 min	30 min or until score of 10	Immediately prior to surgery	Immediately post surgery	At discharge	Next day follow-up	One week follow-up
Written consent	X																
Screening Assessments	X																
Medical History & Physical Examination	X																
12-lead ECG		X												X			
Atropine Score		X		X	X	X	X	X	X	X	X	X				X	
Analgesia Score													X	X			
Surgical Details														X			
Adverse Events															X	X	X
Concomitant Medications	X														X	X	X

The first 12-lead ECG must be done before the study drug is administered, preferably immediately before, and then it will be done again immediately after surgery.

[Sponsor's Table I, "Schedule of Assessments", Item 8, Vol. 1.87, p. 018]

STATISTICAL ANALYSIS

"The primary efficacy endpoint was defined as the time to onset of block suitable for surgery for the per-protocol population. This endpoint was to be calculated as the time from completion to first injection until time of first akinesia score of at least 18."

"The primary analysis population for efficacy was the Intent-to-Treat population. Confirmatory analysis was performed using the per-protocol population. All patients who received study drug were included in the summary of safety data."

"The confirmatory efficacy analysis was to focus on the question of whether levobupivacaine was significantly better than bupivacaine with respect to clinical efficacy."

"The statistical hypotheses behind this trial were as follows:

H_0: The mean difference in the time to anaesthetic suitable for surgery between the treatment groups is less than 5 mm.

H_1: The mean difference in the time to anaesthetic suitable for surgery between the treatment groups is more than 5 mm."

"The primary response variable was to be analysed using analysis of variance (ANOVA) with a term for treatment. Using the error variance from the ANOVA, comparison of the treatment LS Means (ie means adjusted for any imbalance in the design) were to be made using a Student's 't'-test. Estimates of treatment difference and associated 95% confidence interval were to be calculated."

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

[Item 8., Vol. 1.87 p. 030 – 031]

Secondary Efficacy Variable

"The secondary efficacy response variables were defined as follows:

(1) Total volume of study anaesthetic required to achieve adequate block,
(2) Pre-operative analgesia (ie following administration of block) using a 3 point rating scale (0 = no pain, 1 = some pain, 2 = much pain),
(3) Post-operative analgesia (ie immediately after surgery) using a 3 point rating scale (0 = no pain, 1 = some pain, 2 = much pain),
(4) Operating conditions using a 3 point rating scale (0 = excellent, 1 = satisfactory, 2 = poor)"

"Total volume of anaesthetic was to be analysed in an identical way to the primary endpoint (ie ANOVA) using the 'intent-to-treat' population only."

"Pre-operative, post-operative analgesia and operating conditions were to be analysed using a logit model including a term for treatment using the 'intent-to- treat' population only. The interval between achievement of suitable block until the start of surgery was to be considered as a covariate in these analyses. The significance level of the treatment effect was to be investigated using the Wald statistic. The odds ratio of the treatment difference and the associated 95% confidence interval were to be calculated. The logit model assumes proportional odds across the categories of the response variable. The validity of this assumption was to be tested using the score test statistic for goodness- of-fit. If this assumption was clearly not satisfied, non-parametric methods were to be used."

[Item 8, Vol. 1.87, p. 031-032]

PROTOCOL AMENDMENT:

The following amendment was dated 3/10/97. It consisted of following changes:

1. Patient Population
   - The sponsor has increased the age limits from 18-80 to 18 years and over. This change is also seen in the section entitled, "Inclusion Criteria"
2. Study Procedures
   - The sponsor has eliminated the 2 minute rhythm strip from the pre-study evaluations

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 50 patients randomized, all 50(100%) were considered eligible for the Intent-to-Treat population. However, ten patients (2 levobupivacaine and 8 bupivacaine) were excluded from the per-protocol population.

Table 156. Patient – Specific Protocol Violations

PATIENT NUMBER/CENTER	TREATMENT GROUP	VIOLATION	PATIENT TOTALS N (%)
			50 (100) Randomized
Excluded from Safety Population:			
None			**50 (100) Safety Population**
Excluded from Intent-to-Treat:			
None			**50 (100) Intent-to-Treat**
Excluded from Per-Protocol:			
004,008, 019, 021[15]	Bupivacaine	Incorrect Timing of Injections	
006, 020	Levobupivacaine		
005, 018, 025, 021[1], 028	Bupivacaine	Incorrect Volume of Study Drug	
	Levobupivacaine		**40 (80.0) Per-Protocol**
0 (0%) Total Withdrawal			**50 (100%) Total Completed**

[1] Patient experienced both incorrect timing and volume of study drug

Table 157. Patient Disposition

TABLE 1

Patient Recruitment and Exclusions from Populations
Summary Statistics: All Patients

	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE		TOTAL	
	N	%	N	%	N	%
Patients Recruited onto Study	25	100.0	25	100.0	50	100.0
Patients Dosed	25	100.0	25	100.0	50	100.0
Safety Population	25	100.0	25	100.0	50	100.0
Intent-to-Treat Population	25	100.0	25	100.0	50	100.0
Per-Protocol Population	23	92.0	17	68.0	40	80.0

[Sponsor's Table 1, Item 8, Vol. 1. 87 p.051. 107]

Demographics

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

Table 158. Demographics - Intent–to Treat Evaluable Population

TABLE 4.2.1

Demographic Details
Summary Statistics: Intent-to-Treat Population

		0.75% LEVOBUPIVACAINE	0.75% BUPIVACAINE	ALL PATIENTS
Age (Years)	Mean	74.2	72.7	73.4
	SD	10.3	9.9	10.0
	Min	53	51	51
	Max	92	88	92
	N	25	25	50
Height (cm)	Mean	164.2	163.3	163.7
	SD	12.4	11.2	11.7
	Min	137	135	135
	Max	187	185	187
	N	25	25	50
Weight (kg)	Mean	68.33	67.08	67.70
	SD	10.25	15.66	13.12
	Min	50.0	41.0	41.0
	Max	95.0	110.0	110.0
	N	25	25	50

[Sponsor's Table 4.2.1. Item 8, Vol.1.87, p. 056]